A.M.A.

# Archives OF OPHTHALMOLOGY

INDEX NUMBER
IN TWO SECTIONS — SECTION 1

AQUEOUS HUMOR DYNAMICS
JONAS S. FRIEDENWALD, M.D., ET AL.

LENS EXTRACTION IN THE TREATMENT OF GLAUCOMA
EDWARD TAMLER, M.D., ET AL.

CERVICAL SYMPATHETIC GANGLIONECTOMY AND AQUEOUS FLOW
ERIK LINNÉR, M.D., ET AL.

THE EFFECT OF BARBITURATE AND PARALDEHYDE ON AQUEOUS HUMOR DYNAMICS IN RABBITS
HOWARD H. STONE, M.D., ET AL.

ELECTRORETINOGRAPHY IN NIGHT BLINDNESS AND OTHER VITAMIN-A DEFICIENCIES
R. P. DHANDA, M.B., M.S., ET AL.

CATARACTS PRODUCED IN RATS BY 1,4-DIMETHANESULFONOXYBUTANE (MYLERAN)
CYRIL SOLOMON, M.D., ET AL.

CORTICOSTEROIDS IN THE AQUEOUS HUMOR OF THE RABBIT
HARRY GREEN, Ph.D., ET AL.

KERATITIS AND SCLERITIS ASSOCIATED WITH FELTY'S SYNDROME
PAUL J. OSTRIKER, M.D., ET AL.

BIOLOGIC EFFECTS STUDIES ON MICROWAVE RADIATION
D. B. WILLIAMS, B.S., ET AL.

HYSTERICAL AMBLYOPIA
T. F. SCHLAEGEL JR., M.D., ET AL

VISUAL FIELD DEFECTS IN EXOPHTHALMOS ASSOCIATED WITH THYROID DISEASE
THOMAS R. HEDGES JR., M.D., ET AL.

UNEQUAL CORRECTED VISUAL ACUITY AS RELATED TO ANISOMETROPIA
ARTHUR JAMPOLSKY, M.D., ET AL.

TESTING DISTANCE EFFECT ON PHORIA MEASUREMENT AT VARIOUS ACCOMMODATION LEVELS
MATHEW ALPERN, Ph.D.

INTRAOCULAR PENETRATION OF LOCALLY APPLIED STEROIDS
IRVING H. LEOPOLD, M.D., ET AL.

DECEMBER 1955

VOLUME 54 NUMBER 6

SOME EFFECTS OF ULTRASONIC ENERGY ON THE RABBIT EYE
CHRISTOPHER H. MOORE, M.D., ET AL.

ACTION OF ALKALIES ON THE CORNEAL STROMA
W. MORTON GRANT, M.D., ET AL.

*COMPLETE CONTENTS ON FIRST PAGE*

From Ostriker et al., p. 858

AMERICAN MEDICAL ASSOCIATION Publication

# *a scientific corner*

FOR INFORMAL DISCUSSION OF YOUR OPTICAL PROBLEMS

## *The House of Vision Inc.*

CHICAGO

| | | | |
|---|---|---|---|
| EVANSTON | HIGHLAND PARK | OAK PARK | AURORA |
| DES MOINES | MASON CITY | MILWAUKEE | MINNEAPOLIS |
| MUSKEGON | SIOUX CITY | AMES | DAVENPORT |


## TRIFOCALS VERSUS VOCATIONAL BIFOCALS

Trifocals today are very popular, and a great portion of the public seems to adapt to them very readily. However, we had a recent case —a banker—who didn't like his trifocals. Working in conjunction with his ophthalmologist, and discussing his objections to the limitations of the field in both intermediate and reading when applied to his banking tasks, it was decided that we would make him two pairs of bifocals—one pair, his distance correction with a rather small reading segment for street wear; the second pair, his intermediate correction in the distance portion and a large "AA" style Ultex for the reading portion, to be used for his desk work.

If a banker can ever be really happy, this man is now a happy banker. He tells us that in conferences and paper work at his desk he has a wide range of vision and is not too badly fogged while looking into the distance. Further, he has a large reading field for studying the papers and figures he must read so carefully.

The banker also told us that this type of vocational bifocal can change a "do-it-yourself-job" addict from a potential menace to a skilled craftsmen.


***"if it's a lens problem, let's look at it together"***

THE HOUSE OF VISION—MAKERS OF PRESCRIPTION GLASSES FOR THE MEDICAL PROFESSION—WILL BE HAPPY TO FILL *YOUR* PRESCRIPTIONS.

# TABLE OF CONTENTS

VOLUME 54 DECEMBER 1955 NUMBER 6

## ORIGINAL ARTICLES

PAGE

**Aqueous Humor Dynamics** 799
*Jonas S. Friedenwald, M.D., Baltimore, and Bernard Becker, M.D., St. Louis*

**Lens Extraction in the Treatment of Glaucoma** 816
*Edward Tamler, M.D., and A. Edward Maumenee, M.D., San Francisco*

**Cervical Sympathetic Ganglionectomy and Aqueous Flow** 831
*Erik Lunér, M.D., Uppsala, Sweden, and Emile Prijot, M.D., Liège Belgium*

**The Effect of Barbiturate and Paraldehyde on Aqueous Humor Dynamics in Rabbits** 834
*Howard H. Stone, M.D., Baltimore, and Emile L. Prijot, M.D., Liège, Belgium*

**Electroretinography in Night Blindness and Other Vitamin-A Deficiencies** 841
*R. P. Dhanda, M.B., M.S., D.O., Indore, India*

**Cataracts Produced in Rats by 1,4-Dimethanesulfonoxybutane (Myleran)** 850
*Cyril Soloman, M.D., Amos E. Light, M.A., and E. J. De Beer, Ph.D., Tuckahoe, N. Y.*

**Corticosteroids in the Aqueous Humor of the Rabbit** 853
*Harry Green, Ph.D., Henry S. Kroman, M.S., and Irving H. Leopold, M.D., Philadelphia*

**Keratitis and Scleritis Associated with Felty's Syndrome** 858
*Paul J. Ostriker, M.D., Marilyn Ostriker, M.D., and Mortimer A. Lasky, M.D., Brooklyn*

**Biologic Effects Studies on Microwave Radiation** 863
*D. B. Williams, B.S., Randolph Field, Texas, J. P. Monahan, M.D., London, England, W. J. Nicholson, B.S., Kirtland Air Force Base, N. Mex., and J. J. Aldrich, M.S., Randolph Field, Texas*

**Hysterical Amblyopia** 875
*T. E. Schlaegel Jr., M.D., Indianapolis, and F. V. Quilala, M.D., Quezon City, Philippines*

**Visual Field Defects in Exophthalmos Associated with Thyroid Disease** 885
*Thomas R. Hedges Jr., M.D., and Harold G. Scheie, M.D., Philadelphia*

**Unequal Corrected Visual Acuity as Related to Anisometropia** 893
*Arthur Jampolsky, M.D., Bernice C. Flom, O.D., Frank W. Weymouth, Ph.D., and Lincoln E. Moses, Ph.D., San Francisco*

**Testing Distance Effect on Phoria Measurement at Various Accommodation Levels** 906
*Mathete Alpern, Ph.D., Ann Arbor, Mich.*

**Intraocular Penetration of Locally Applied Steroids** 916
*Irving H. Leopold, M.D., John L. Sawyer, and Harry Green, Ph.D., Philadelphia*

**Some Effects of Ultrasonic Energy on the Rabbit Eye** 922
*Christopher H. Moore, M.D., J. F. Herrick, Ph.D., and Theodore G. Martens, M.D., Rochester, Minn.*

**Action of Alkalies on the Corneal Stroma** 931
*W. Morton Grant, M.D., and Harold L. Kern, Sc.D., Boston*

## CLINICAL NOTES, NEW INSTRUMENTS AND TECHNIQUES

**A New Contact Lens Electrode for Clinical Electroretinography** 940
*Jerry Hart Jacobson, M.D., New York*

## ANNUAL REVIEWS

**Glaucoma** 941
*Joseph S. Haas, M.D., Chicago*

## REGULAR DEPARTMENTS

**News and Comment** ..... 874, 915, 939, 956, 957

**Books** ..... 959

# A. M. A.
# ARCHIVES OF OPHTHALMOLOGY

VOLUME 54 DECEMBER 1955 NUMBER 6


COPYRIGHT, 1955, BY THE AMERICAN MEDICAL ASSOCIATION


Continuing the Publication

FOUNDED BY HERMAN KNAPP, 1869



## EDITORIAL BOARD

FRANCIS HEED ADLER, Chief Editor

313 South Seventeenth Street, Philadelphia 3

WILLIAM ZENTMAYER, Philadelphia

W. L. BENEDICT, Rochester, Minn.

KENNETH C. SWAN, Portland, Ore.

WILLIAM F. HUGHES Jr., Chicago

DAVID G. COGAN, Boston

JONAS S. FRIEDENWALD, Baltimore

JOHN H. DUNNINGTON, New York

ASSOCIATES:

Alson E. Braley
F. Phinizy Calhoun Jr.
A. Gerard DeVoe
Trygve Gundersen
Joseph S. Haas
John E. Harris
John M. McLean
Paul W. Miles
Frank Payne
Ludwig von Sallmann
Henry P. Wagener
Maynard C. Wheeler

AUSTIN SMITH, Editor, A. M. A. Scientific Publications

GILBERT S. COOPER, Managing Editor, Specialty Journals



## AMERICAN MEDICAL ASSOCIATION
### Scientific Publications

**The Journal of the American Medical Association.** Weekly. Annual Subscription Price, $15.00.

**Quarterly Cumulative Index Medicus.** Issued Twice a Year. Subscription Price, Calendar year, $20.00.

### A. M. A. Specialty Journals
#### Monthly

**A. M. A. Archives of Internal Medicine.** Paul S. Rhoads, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.

**A. M. A. Archives of Dermatology.** Herbert Rattner, M.D., Chief Editor, 104 S. Michigan Ave., Chicago. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

**A. M. A. Archives of Ophthalmology.** Francis Heed Adler, M.D., Chief Editor, 313 S. 17th St., Philadelphia 5. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

**A. M. A. Archives of Surgery.** Waltman Walters, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.25.

**A. M. A. American Journal of Diseases of Children.** Robert B. Lawson, M.D., Chief Editor, 1000 N.W. 17th St., Miami 36, Fla. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

**A. M. A. Archives of Pathology.** Paul R. Cannon, M.D., Chief Editor, Department of Pathology, University of Chicago, The School of Medicine, 950 E. 59th St., Chicago 37. Price, $8.00; Canada, $8.50; Foreign, $9.25; individual copy, $1.00.

**A. M. A. Archives of Neurology and Psychiatry.** Tracy J. Putnam, M.D., Chief Editor, 450 N. Bedford Drive, Beverly Hills, Calif. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

**A. M. A. Archives of Otolaryngology.** George M. Coates, M.D., Chief Editor, 1721 Pine St., Philadelphia 3. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

**A. M. A. Archives of Industrial Health.** Prof. Philip Drinker, Chief Editor, Dept. of Industrial Hygiene, Harvard University School of Public Health, 55 Shattuck St., Boston 15. Price, $8.00; Canada, $8.50; Foreign, $9.00; individual copy, $1.00.

Check, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.



Published Monthly by

AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Feb. 7, 1929, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

A Very
Merry Christmas
and
a Fine, Full,
New Year
Continental
INDIANAPOLIS

## Instructions to Contributors

Communications regarding editorial management, subscriptions, reprints, etc., should be addressed to Specialty Journals, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor of the Specialty Journal concerned. Articles are accepted for publication on condition that they are contributed solely to that journal.

An original typescript and the first carbon of an article should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. An article in English by a foreign author should be accompanied by a draft in the author's mother tongue. Improvised abbreviations should be avoided.

The main title of an article may not contain more than seventy characters and spaces; a subtitle may be of any length. The subtitle should be sufficiently detached from the main title that a punctuation mark as strong as a colon can be used in the Table of Contents to separate it from the main title; it must not begin with "with."

The author's name should be accompanied by the highest academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

Typographic considerations necessitate that the first paragraph of an article contain not fewer than thirty words. A Case Report must be preceded by an introductory paragraph containing at least thirty words before the details of the case are given.

Material quoted from another publication must be quoted exactly if the original is in English—spelling, capitalization, punctuation, etc., unchanged. Material taken largely from another publication must be credited to the original author, whether quoted exactly or merely abstracted. If such material is quoted indirectly, the author must be careful to leave no complete sentence of the original unaltered. Use of uncredited quotations will be sufficient cause for rejection of an article.

Each article should be accompanied by a summary in the present tense, presenting the main points of the article, but in somewhat more generalized terms than in the article itself.

If it is necessary to publish a recognizable photograph of a person, the photograph must be accompanied by written permission of the subject himself if an adult, or of the parents or guardian if a child, to publish his photograph. An illustration which has been published in another publication must be accompanied by written permission from the author and the original publisher to reproduce it in an A. M. A. Specialty Journal.

The maximum illustration allowance is ten illustrations within a total of 100 sq. inches or 8100, whichever is of greater advantage to the author. When no restrictions are placed by the author upon cropping, reducing, and grouping, the publisher is often able to use twenty or more illustrations in one article with the 8100 allowance. Submit sharp prints of the following sizes, 2¼″ wide × 2½″ or 3½″ high, 3¼″ wide × 2½″ high, and 5¼″ or 7″ wide × 3½″ high, to minimize reduction and/or cropping. Oversized originals should be photographed and a print submitted. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author.

Any cut-off marks should be made on the margins or mountings rather than on the illustration itself. Charts and drawings should be in black ink on hard, white paper. Lettering must be large enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, an abbreviated title of the article, and top plainly indicated. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. IT IS PREFERRED THAT ILLUSTRATIONS BE UNMOUNTED.

References to the literature should be numbered in the order in which they are referred to in the text or listed in alphabetical order without numbers. A chronological arrangement, with all entries for a given year alphabetized according to the surname of the first author, may be used if preferred. References should be typed on a special page at end of manuscript. They should conform to the style of the Quarterly Cumulative Index Medicus, and must include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. Names of periodicals should be given in full or abbreviated exactly as in the Quarterly Cumulative Index Medicus. Reference to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication. Titles of foreign articles, if originally in a generally known Romance or Germanic tongue, must either all be in English translation or all be in the original language. Titles in other languages must be translated. The author must assume responsibility for the accuracy of foreign titles.

Matter appearing in the A. M. A. Specialty Journals is covered by copyright, but as a rule no objection will be made to its reproduction in a reputable medical journal if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the A. M. A. Specialty Journals, or in any other publications issued by the Association, will not be permitted.

**AMERICAN MEDICAL ASSOCIATION**

**535 North Dearborn Street** **Chicago 10**

# Wishing you a Merry Christmas and New Year

## PROSPERITY

1 Orthogon series of corrected lenses—
for maximum patient satisfaction.

2 Panoptik bifocals and trifocals—
for natural, youthful visual habits.

3 Ray-Ban lenses—for finest glare absorption.
Soft-Lite—cosmetic fleshtone tint.

4 Frames and mountings in pace-setting styles.

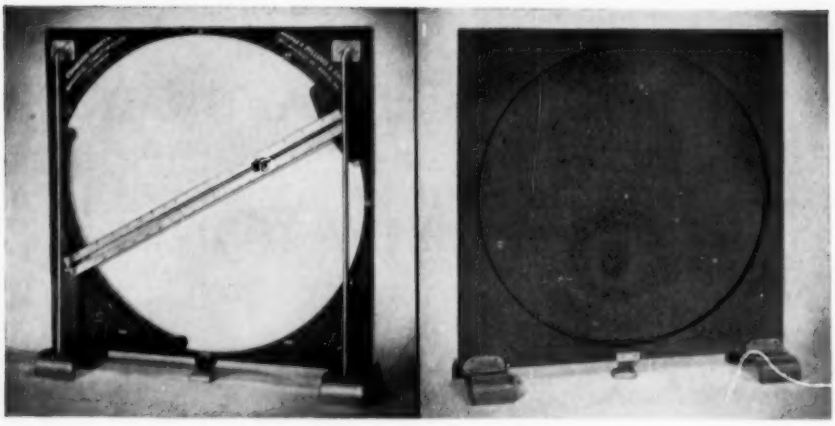
5 Gold filled materials of unexcelled precision.

6 Seasoned plastics in distinctive, modern colors.

*Neat, compact, legible—the Bausch & Lomb Calendar has become a popular feature in professional offices throughout the nation. It displays each month's calendar from both sides. If you haven't received your 1956 edition, just write us on your letterhead: Bausch & Lomb Optical Company, Dept. F-068, Rochester 2, N. Y.*

BAUSCH & LOMB

SINCE B&L 1853



*Conover-Spaeth**

# MAGNETIC CAMPIMETER


***EDMUND B. SPAETH, M.D.**

**PHILADELPHIA, PA.**


This new precision instrument gives *accurate* determinations and correct configuration of the visual field with great savings of time and effort.

The Conover-Spaeth Campimeter is 24" square. It is placed on a table with the patient seated in front, his eye positioned 10½" from the central fixation point. The operator, standing behind the screen, facing the patient and looking directly into the patient's eye, is able to detect the slightest wavering. The test object is introduced to the visual field from a "Concealment Circle" and is controlled by a magnet from the back of the campimeter. The patient is not able to anticipate or even guess on which radius or from which side, right or left, the test object will appear.

This assures accuracy and eliminates time-consuming rechecking.

The back of the campimeter is clearly marked in degrees of the circle and angles of vision to conform to the standard Berens chart. Each radius tested is immediately entered on the chart . . . No markers to be placed or removed.

The time saved in each examination creates opportunities for more "fields" or other office work.

**√ ABSOLUTE ACCURACY**

**√ FAR FASTER**

Write for detailed information.

MANUFACTURER AND GENERAL DISTRIBUTOR

GEORGE P. **Pilling** & SON CO.

**3451 WALNUT STREET PHILADELPHIA**

*HEADQUARTERS FOR INSTRUMENTS FOR OTORHINOLARYNGOLOGY*

# HydroCortone®

(HYDROCORTISONE, MERCK)

*"...effective in some cases in which cortisone was comparatively ineffective..."*[1]

**MAJOR ADVANTAGES: Greater anti-inflammatory action than cortisone; smaller doses produce equivalent therapeutic response.**

In the treatment of ocular disease, HYDROCORTONE "has proved effective in some cases in which cortisone was comparatively ineffective."[1] "The ideal treatment schedule in any severe intraocular inflammation, especially of the posterior segment, consists of an initial course of systemic therapy."[1] When the condition improves, local therapy may be adequate for control.

"Approximately 60 mg. daily has proved to be a good maintenance dose in chronic cases. There has been a surprising freedom from side effects such as Cushing's syndrome."[1]

**INDICATIONS:** Anterior segment inflammatory eye diseases and posterior segment inflammatory eye diseases.

**SUPPLIED: ORAL** — HYDROCORTONE Tablets: 20 mg., bottles of 25, 100, and 500 tablets; 10 mg., bottles of 50, 100, and 500 tablets; 5 mg., bottles of 50 tablets. **OPHTHALMIC** — Sterile Suspension of HYDROCORTONE Acetate: 0.5% and 2.5%, 5-cc. vials. Ophthalmic Ointment of HYDROCORTONE Acetate: 1.5%, 3.5-Gm. tubes.

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

**REFERENCE:** 1. Gordon, D.M., *Am. J. Ophth.* **37**:533, April 1954.

Rx

QUALITY SERVICE

Technical skills and services that will never let you down

DOW

## Top-Grade Technical Performance

. . . a Safeguard for Your Professional Skills and Judgment.

¶Your prescriptions, conceived from your rich fund of scientific knowledge laboriously developed through years of study, training and experience, are at the mercy of the dispensers who interpret them. They will be safe in the hands of Dow seasoned craftsmen, whose devotion to the exacting standards which your professional reputation demands, and which our firm has consistently maintained throughout its 31 years of existence, is a guarantee of complete patient satisfaction.

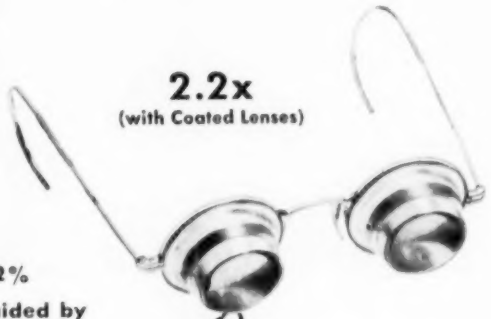
**DOW OPTICAL CO.**

*W. E. DOW, Pres.*

Chicago, Ill. Bloomington, Ill.

# LOW VISUAL ACUITY?

**Many Cases with visual acuity as low as 2% can be aided by**



**2.2x**
**(with Coated Lenses)**

*Spectel*
TELESCOPIC SPECTACLES

These successful aids to subnormal vision are available in two powers, 1.7 or 2.2 diameters. Spectel telescopic spectacles are fitted without complicated equipment or procedures. Trial sets are moderate in price.

Complete details in Bulletin 302, available from your optical supply house or direct from us.

**KOLLMORGEN** *Optical* **CORPORATION**

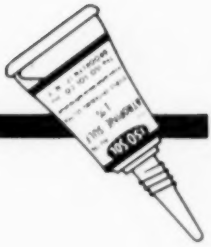
PLANT: NORTHAMPTON, MASSACHUSETTS

NEW YORK OFFICE: 30 CHURCH ST., NEW YORK 7, N. Y.

Distributed in Canada by Imperial Optical Company

# New!

ISO-SOL



# Dropperettes®

Disposable, transparent 1cc plastic tubes with dropper nozzle and replaceable cap.

NON-FLAKING UREA CAP TO KEEP DUST OFF NOZZLE
BLIND TIP FOR HERMETIC SEALING
TRANSPARENT WALL AS AN EXTRA CHECK AGAINST POSSIBLE FOREIGN BODY CONTAMINATION
AIRTIGHT SEAL

- Sterile - Fully Potent
- Hermetically Sealed
- Controlled Dropping
- Salvageable Remainder
- Light - Unbreakable
- Space Saving
- For Operating Room
  Hand Bag
  Treatment Stand

Packaging - Boxes of 10 and 25.

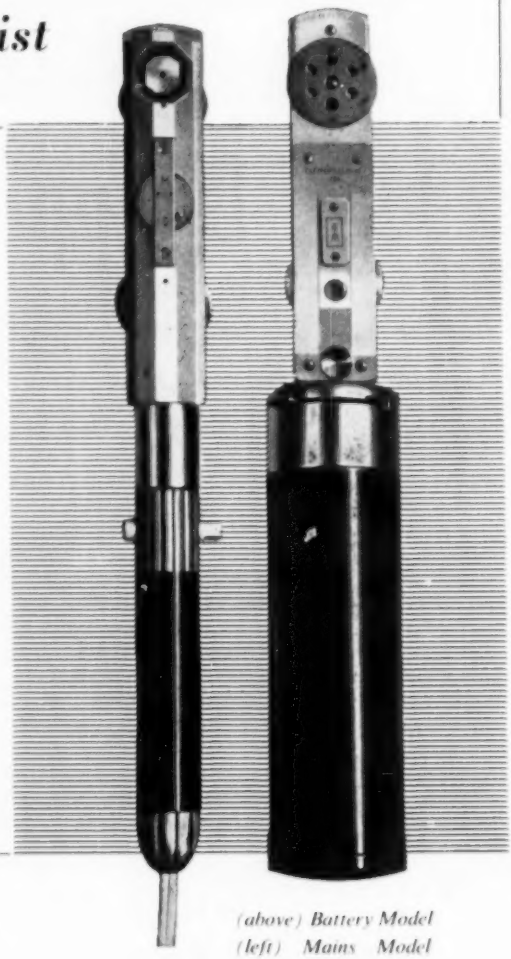
Atropine 1%, Tetracaine ½%, Fluorescein 2%, others.

*Send for free sample box of Dropperettes*

THE ISO-SOL CO., INC., BROOKLYN 17, N. Y.

# A NEW OPHTHALMOSCOPE

## *for the specialist*



### MAINS OR BATTERY OPERATED

This new instrument is recommended for difficult and border-line cases, and particularly where the pupil is small or where opacities are present. It combines optical and mechanical precision, is durable and easy to handle and gives maximum homogeneous illumination. Although designed primarily for direct use and for the usual critical examination of the cornea, lens, vitreous, etc., indirect ophthalmoscopy can be effected under dark room conditions. It will not measure refraction, neither can it be used for Slit Lamp examination, these very important functions being better performed by specially designed instruments.

*For descriptive leaflet please write:-*

*(above) Battery Model*
*(left) Mains Model showing head in obverse and reverse*

**CLEMENT CLARKE** of ENGLAND

GUILD OPTICIANS

63 WIGMORE STREET, LONDON, W.1. ENGLAND

*Cablegrams: Clemclarke, London*

# *Thanks . . . and Best Wishes*

## *For a Happy Holiday Season*

Christmas gives us a *special* opportunity
to pause and say *"thank you"*
to our many loyal friends.

Your confidence in BENSON OPTICAL CO.
is deeply appreciated.

**Since 1913** **Benson** OPTICAL COMPANY **Executive Offices • Minneapolis 2, Minn.**

COMPLETE LABORATORIES CONVENIENTLY LOCATED IN UPPER MIDWEST CITIES

WIES Chalazion Forceps, with flattened top, to allow introduction deep into the fornix. Transverse serrations prevent slippage.
Stainless Steel $11.00 each

NEW
CHALAZION FORCEPS
BY LAWTON

The LAWTON Company
425 FOURTH AVENUE NEW YORK 16, N. Y.

LORDAN Chalazion Forceps, with pointed jaw, to facilitate access to the smaller types of chalazia either at the inner or external canthus.
Stainless Steel $10.50 each

Available Only Through Authorized Surgical Supply Dealers

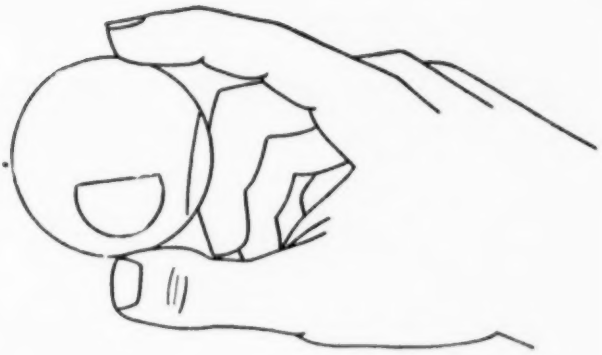
OPHTHALMIC INSTRUMENTS
OF PRECISION

Theodore Hamblin Ltd

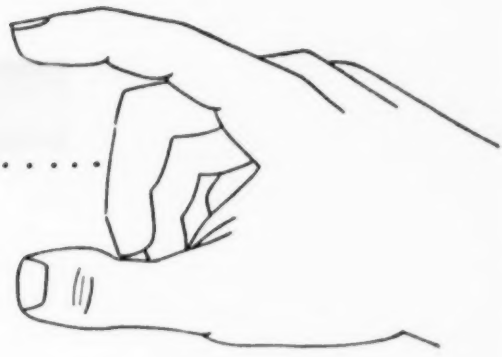
GUILD Rx OPTICIANS

15 WIGMORE STREET,
LONDON, W.I.
ENGLAND.

NOW YOU SEE IT.....



NOW YOU DON'T.....



OOPS! WHAT'S THIS?

VISION-EASE

# "LACRILENS"®

## is a safe lens

The test of time proves that the "LACRILENS"® contact lens can be worn for long periods of time in aphakia and in all sports, including swimming. *Write For Brochure*

**Obrig Laboratories Inc.**
49 East 51st Street, New York 22, N. Y.

*Manufacturers of all types of Contact Lenses*
Branches in
PHILADELPHIA • MONTREAL • JOHANNESBURG

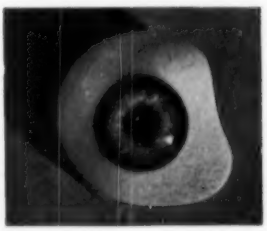
Obrig®

---

**Specialists in ALL TYPES of Plastic and Glass Artificial Human Eyes Exclusively**

MADE TO ORDER IN OUR OWN LABORATORY

***Doctors are invited to visit***



**REFERRED CASES CAREFULLY ATTENDED AND SATISFACTION GUARANTEED**

*EYES ALSO FITTED FROM STOCK*

**Plastic or Glass Selections Sent on Memorandum upon Request**

*Implants and Plastic Conformers in Stock*

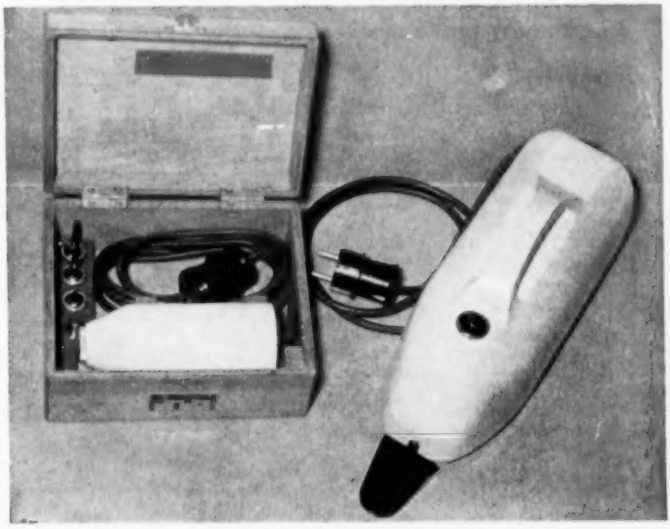
# FRIED AND KOHLER, INC.

665 FIFTH AVENUE
near 53rd St.

NEW YORK, N. Y.
Tel. ELdorado 5-1970

storz
*Surgical Instruments*

# NEW • LIGHT • POWERFUL



## STORZ ATLAS **Hand Eye Magnet**

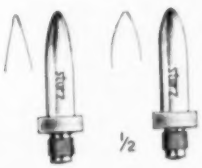
**E-6650**—Eye Magnet, Atlas: complete with four tips in wooden case and separate rectifier with footswitch. Small size for maneuverability and ease of handling. The magnet weighs 4.6 lbs. The rectifier with footswitch weighs 8.7 lbs. The type of tip selected is dependent on the position of the splinter. For strongest pulling power, the large cone tip is applied. More effective results are obtained by stepping on the footswitch repeatedly to get short interrupted pull rather than a long steady pull.

**Power:** The absolute pulling power at the flange is 12.5 kg. or 28 lb. The ball jump power is 38.5 mm. The handling is not interfered with by strong directional pulls.

**Advantages...** **Small size—Light weight—POWER!** —

Made for 110 volt, 60 cycle, alternating current. If other current or voltage is desired, please specify. Uses 150 watts. Developed and tested at the University Eye Clinic in Kiel.

**Complete—$149.50**




E-6654 Magnet Tip, Intra-ocular, BONACCOLTO: small. $3.75

E-6655 Magnet Tip, Intra-ocular, BONACCOLTO: large. $3.75

These tips not included with magnet. Please order separately.

Storz Instruments are available from Storz salesmen only. We do not distribute under any other name or trademark.

*Order directly from*

*Storz Instrument Company*

4570 Audubon Ave. St. Louis 10, Mo.

A NEW SERIES IN

# SEX EDUCATION

## Titles in the new series

- PARENTS' PRIVILEGE
  for parents of young children of pre-school and early school age
- A STORY ABOUT YOU
  for children in grades 4, 5, and 6
- FINDING YOURSELF
  for boys and girls of approximately junior high school age
- LEARNING ABOUT LOVE
  for young people of both sexes (about 16 to 20 years of age)
- FACTS AREN'T ENOUGH
  for adults who have any responsibility for children or youth that may create a need for an understanding of sex education

### PRICES

Note: Discounts apply to quantities of any single title, or to quantities of sets.

| Quantity | Discount | Price |
|---|---|---|
| 1 | — | $ .50 |
| 10 | 10% | 4.50 |
| 25 | 30% | 8.75 |
| 50 | 40% | 15.00 |
| 100 | 50% | 25.00 |
| 1000 | 60% | 200.00 |

Set of 5 titles, $2.25

**Distributed By**

**Order Department**

**AMERICAN MEDICAL ASSOCIATION**

535 N. Dearborn St.

Chicago 10, Ill.

### ORDER BLANK

Enclosed is $_____ (no stamps) for the following pamphlet(s):

| Title | Quantity |
|---|---|
| 1. PARENTS' PRIVILEGE | |
| 2. A STORY ABOUT YOU | |
| 3. FINDING YOURSELF | |
| 4. LEARNING ABOUT LOVE | |
| 5. FACTS AREN'T ENOUGH | |
| Complete set of five | |

Please send pamphlet(s) to:
(Please Print)

Name_____

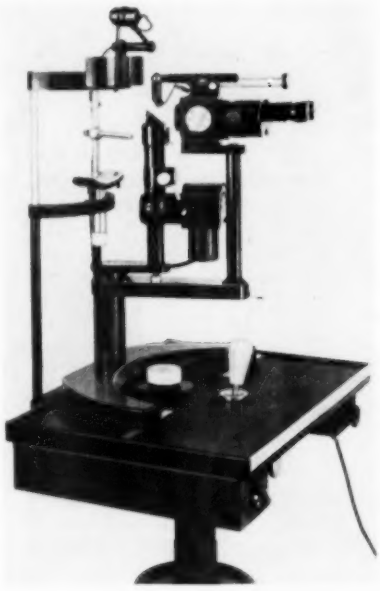
Street_____

City_____

Zone_____ State_____

OP 12-55

# SLIT LAMP APPARATUS



MADE BY

CARL ZEISS

IN WEST GERMANY

**ON INSTRUMENT TABLE OR COMPOUND STAGE, the latter designed for electric tables or refracting units.**

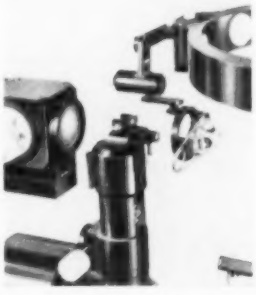
Requires no adjustments. The slit lamp can be swung past the corneal microscope without interruption of observation.

Can be set for five different magnifications by simply turning a knob, without changing objectives, eyepieces, or the working distance.

Maximum brilliance of the illuminating rays and sharpest possible definition of the microscope images.

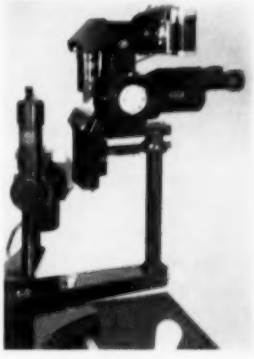
Supplementary equipment, such as Hruby lens, gonioscope, photo attachment, etc., are available.

## ACCESSORIES



ATTACHMENT FOR GONIOSCOPY (left) consisting of: 4-mirror contact glass with handle, carrier and rotating device. Rotatable prism in mount. To keep lid apart during examination we offer one each small and large lid separator.

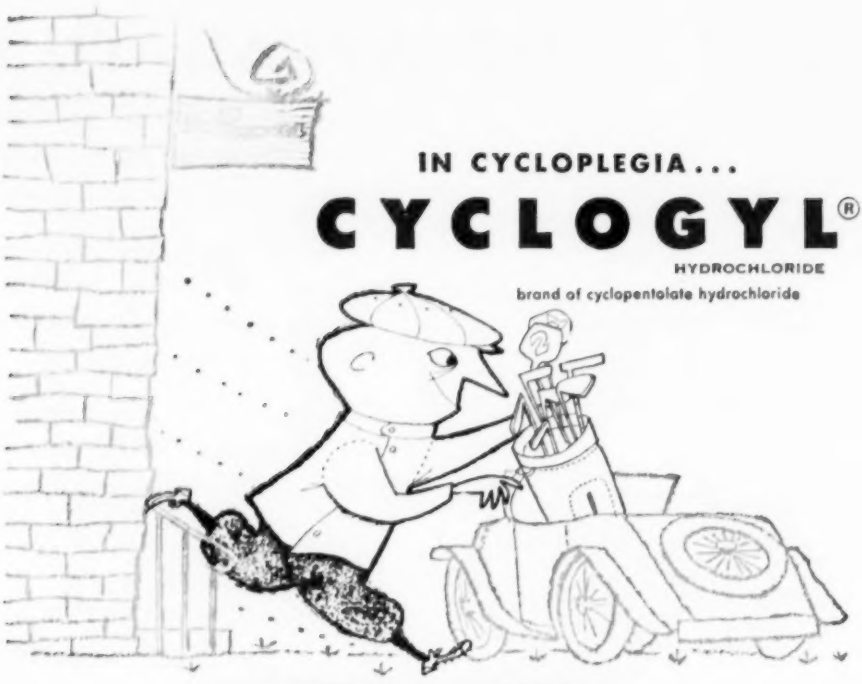
PHOTO ATTACHMENT (right) with electronic flash equipment to automatically photograph anterior segment of eye at magnifications of 1x or 2x.



***Write for literature***

**CARL ZEISS, INC.,** 485 Fifth Avenue, New York 17, N.Y.

*Guaranteed Uninterrupted Repair Service*



## IN CYCLOPLEGIA . . .

# CYCLOGYL®

HYDROCHLORIDE

brand of cyclopentolate hydrochloride

## SAVES TIME

**. . . for you . . . with rapid onset of action**

**. . . for your patients . . . with rapid recovery**

"Cyclopentolate hydrochloride . . . produces a rapid [30 to 60 minutes], intense cycloplegia and mydriasis of moderate duration . . . and is effective in highly pigmented irises and for persons of all ages." *New and Nonofficial Remedies, Philadelphia, J. B. Lippincott Company, 1954, p. 189.*

Cyclogyl has shown outstanding qualities in 1035 cases.[1]
(Incorporates work of 11 previous investigators)

| Compound | Dosage and Administration (drops) * | Diopters of Residual Accommodation | Spontaneous Recovery (in hr.) |
|---|---|---|---|
| Cyclogyl 0.5% | 2 | 1.10 | 24† |
| Homatropine 2% or 4% | 2 | 2.00 | 48 |

*Successive drops at five minute intervals. †Recovery time reduced to six hours after one percent pilocarpine.
*1. Gordon, D. M., and Ehrenberg, M. H.: Am. J. Ophth. 38:831 (Dec.) 1954.*

"the chief handicap of maximum cycloplegia, namely its incapacitating effect, is minimized . . ." *Gettes, B. C.: A.M.A. Arch. Ophth. 51:467 (Apr.) 1954.*

Cyclogyl, "by virtue of its brevity, rapidity of action, and consistent depth of cycloplegia, will be [a drug of choice] for routine refraction . . ." *Ehrlich, L. H.: New York J. Med. 53:3015 (Dec. 15) 1953.*

**Dosage:**
Cycloplegia — One drop 1.0%, in each eye (or two drops of 0.5%) produces maximal cycloplegia in 30-60 minutes. Recovery time is normally 4-12 hours spontaneously. Pilocarpine reduces recovery time. In deeply pigmented eyes, 2 drops of 1.0% in each eye, instilled 10 minutes apart, achieves satisfactory cycloplegia in 98% of cases.
Mydriasis — One or two drops of 0.5% in each eye.

Samples and Literature on request.

**Supplied:**
Sterile ophthalmic solution in Gifford's Buffer (pH 6.0)
0.5% Solution — 15 cc Dropper Bottles
1.0% Solution — 15 cc Dropper Bottles
2 cc Dropper Bottles

Schieffelin & Co. Since 1794
Pharmaceutical and Research Laboratories
New York 3, N. Y.

A.M.A. Archives of
OPHTHALMOLOGY

*The following paper was submitted to the A. M. A. Archives of Ophthalmology by Dr. Jonas Friedenwald shortly before his untimely death, on November 6.*

*It is the last of many contributions he made to the Archives. It seems fitting at this time that the Editorial Board should announce with great sorrow the passing of a member whose name will endure throughout the years as one of America's greatest ophthalmologists. An obituary will appear in the January issue.*

FRANCIS HEED ADLER, M.D.

# Aqueous Humor Dynamics

## Theoretical Considerations

JONAS S. FRIEDENWALD, M.D., Baltimore
and
BERNARD BECKER, M.D., St. Louis

In a series of papers, Kinsey [1] developed the technique of posterior chamber taps and has applied this technique both to the study of steady-state relations between plasma and posterior and anterior chamber concentrations of normal constituents [2] and to the analysis of aqueous humor dynamics as disclosed by the changing concentrations of a test substance in anterior and posterior chambers following the injection of such a test substance into the animal.[2]

To express the rate of change of concentration of the test substance in the anterior chamber, Kinsey and Palm have used the equation

$$\frac{dC_a}{dt} = K_f(C_\pi - C_a) + K_d(C_p - C_a) \qquad (1)$$

where $C_\pi$, $C_a$, and $C_p$ represent, respectively, the momentary concentrations of the test substance in the fluid passing through the pupil ($\pi$), in the anterior chamber ($a$) and in the plasma ($p$). $K_f$ represents the rate of flow per minute as a fraction of the volume of anterior chamber; $K_d$ represents the corresponding rate of diffusional exchange between anterior chamber and plasma. Thus, the rate of change of anterior chamber concentration $\frac{dC_a}{dt}$ is expressed as the algebraic sum of inflow $K_fC_\pi$, outflow $-K_fC_a$, and diffusional exchange $K_d(C_p - C_a)$.

It is the purpose of the present paper to examine the factors involved in what, at present, can be considered required in any reasonably complete theory of aqueous humor dynamics. The analysis will proceed in two parts. In the first we shall

Received for publication Sept. 26, 1955.
From the Wilmer Ophthalmological Institute of The Johns Hopkins Hospital.
This study was supported in part by a grant from the Kellogg Foundation.

[2] References 1 and 2.

consider the assumptions involved in Equation (1) and attempt to establish, if possible, the limits within which these assumptions are valid. In the second we shall show that under certain further limitations this equation may be integrated. The application of the integrated equation to experimental data furnishes a further test of the validity of the underlying assumptions.

Equation (1) is closely related to the expression originally used by Kinsey and co-workers in developing the theory of diffusion plus flow as applied to aqueous humor dynamics.† In all preceding work, however, it had to be assumed for the purposes of simplification that the concentration, $C_\pi$, of the test substance in the fluid entering the anterior chamber via the pupil was constant so long as the plasma concentration was constant. Kinsey and Palm's new contribution consists in using posterior chamber taps as an assay of the momentary concentrations $C_\pi$. Even if fluid entering the posterior chamber contains a fixed concentration of the test substance as long as the plasma concentration is held fixed, the concentration in a mixed sample of posterior chamber fluid cannot be expected to be constant, because the volume of the posterior chamber is not negligibly small and time is required for its filling with the newly entering fluid. Moreover, at the beginning of such experiments as Kinsey and his co-workers have performed the concentration of the test substance in the vitreous and lens is zero, while at the end of the experiment these concentrations must have reached some steady-state values. The building up of concentrations in these "posterior reservoirs" must occur in part at the expense of test substance lost from the posterior chamber. Thus, there are sound a priori reasons for expecting the posterior chamber concentration, and hence also the pupillary concentration of the test substance, to vary during the course of the experiment. Previous investigators have not been unaware of these complications. However, until the technique of posterior chamber taps was developed, such considerations could be of only theoretical interest.

## PART I

### 1. Linear Relations

The experimental data of Kinsey and Palm bear out these a priori expectations and reveal the complicated course of concentration change in the posterior chamber. The general validity of Equation (1) is strongly supported by the finding that with each of two different test substances—radioactive sodium and thiocyanate—Kinsey and Palm obtained an essentially identical estimate of the rate of aqueous flow, $K_f$. If we divide Equation (1) by $(C_v - C_a)$, we obtain

$$\frac{dC_a}{(C_v - C_a)dt} = K_f \frac{C_\pi - C_a}{C_v - C_a} + K_d \qquad (2)$$

This equation is evidently of the form

$$Y = K_f X + K_d$$

Since $X$ and $Y$ can be determined from the experimental data, one test of the validity of Equation (1) is the linearity of a plot of $X$ vs. $Y$.

Kinsey has supplied us with the experimental data to make this test possible. In order to be independent of previous efforts at curve fitting, we have made our own estimates of the smoothed curves which seem best to fit the data. The results of this curve fitting are given in Table 1. Curves were drawn representing the course of the anterior chamber concentration with respect to time, and the slope of these curves at different time values was estimated graphically. The results

† References 5 and 6.

TABLE 1.—*Turnover Rate of Sodium and Thiocyanate in Rabbit Eyes*

| Time, Min. | SCN | | | Na | | |
|---|---|---|---|---|---|---|
| | $C_{\bar{a}}$ | $C_a$ | $\frac{dC_a}{dt}$ | $C_{\bar{a}}$ | $C_a$ | $\frac{dC_a}{dt}$ |
| 0 | 0 | 0 | .... | 0 | 0 | .... |
| 5 | 13 | 4 | .... | 1 | 2 | .... |
| 10 | 20 | 8 | 0.76 | 10 | 5 | 0.62 |
| 20 | 30 | 15 | 0.76 | 35 | 14 | 1.00 |
| 30 | 35 | 23 | 0.76 | 46 | 26 | 1.06 |
| 40 | 39 | 30 | 0.75 | 51 | 36 | 0.96 |
| 50 | 41 | 36 | 0.67 | 54 | 44 | 0.79 |
| 60 | 43 | 41 | 0.55 | 56 | 50 | 0.60 |
| 70 | 44 | 46 | 0.46 | 58 | 56 | 0.53 |
| 80 | 45 | 49 | 0.36 | 60 | 61 | 0.44 |
| 90 | 46 | 51 | 0.28 | 61 | 65 | 0.36 |
| 100 | 47 | 54 | 0.25 | 62 | 68 | 0.28 |
| 120 | 48 | 57 | 0.21 | 65 | 72 | 0.20 |
| 140 | 50 | 61 | 0.18 | 65 | 76 | 0.14 |
| 160 | 51 | 63 | 0.15 | 69 | 78 | 0.12 |
| 180 | 52 | 64 | 0.08 | 71 | 80 | 0.10 |
| 200 | 53 | 65 | 0.03 | 73 | 82 | 0.09 |
| 225 | 54 | 66 | .... | 75 | 84 | .... |
| 250 | 55 | 67 | .... | 78 | 86 | .... |
| 275 | 56 | 68 | .... | 80 | 87 | .... |
| 300 | 57 | 69 | .... | 81 | 88 | .... |
| ∞ | 63 | 74 | .... | 99 | 98 | .... |

are shown in the columns headed $\frac{dC_a}{dt}$ in Table 1. $C_p$ is arbitrarily assumed to be 100.

From the data of Table 1, values for $X$ and $Y$ have been computed:

$$X=\frac{C_{\bar{a}}-C_a}{C_p-C_a} \qquad Y=\frac{dC_a}{(C_p-C_a)dt} \tag{3}$$

The resulting plots are shown in Figure 1. In these plots data from the first 30 minutes of the experiments are omitted, since in the experiments a time lag of this order was required for the plasma levels of the test substance to be stabilized. Further discussion concerning the interpretation of data obtained early in the time course of these experiments will be given below. The application of this method of analysis to the data is less satisfactory in the case of sodium than in that of thiocyanate. With sodium the steady-state concentration levels both for the anterior and for the posterior chamber are very nearly equal to the plasma concentration. Consequently, as the experiment progresses, the differences $(C_{\bar{a}}-C_a)$ and $(C_p-C_a)$ both tend to become small, and the errors in their estimates percentually large. In spite of these difficulties, it will be seen that the data do fall reasonably well on straight lines for both substances. The slope of these lines gives estimates of the coefficient of flow $K_f$ and have the value of 0.014 from the sodium data and 0.017 from the thiocyanate data. The mean value of 0.0155 would represent both sets of data within the experimental range of uncertainty.

The estimates compare well with the estimates reached by Kinsey and Palm[4] through the application of numerical integration to their data. This is no wonder, since the two methods are similar ways for finding values of $K_f$ and $K_d$ to fit Equation (1) to the same experimental data. In the method of numerical integration arbitrary values of $K_f$ and $K_d$ are assumed for trial, and $\frac{dC_a}{dt}$ is then calculated by applying Equation (1) to the experimental data. Using these estimates of the rate of change of the anterior chamber concentration for successive short time intervals, one reconstructs stepwise the time course of the anterior chamber con-

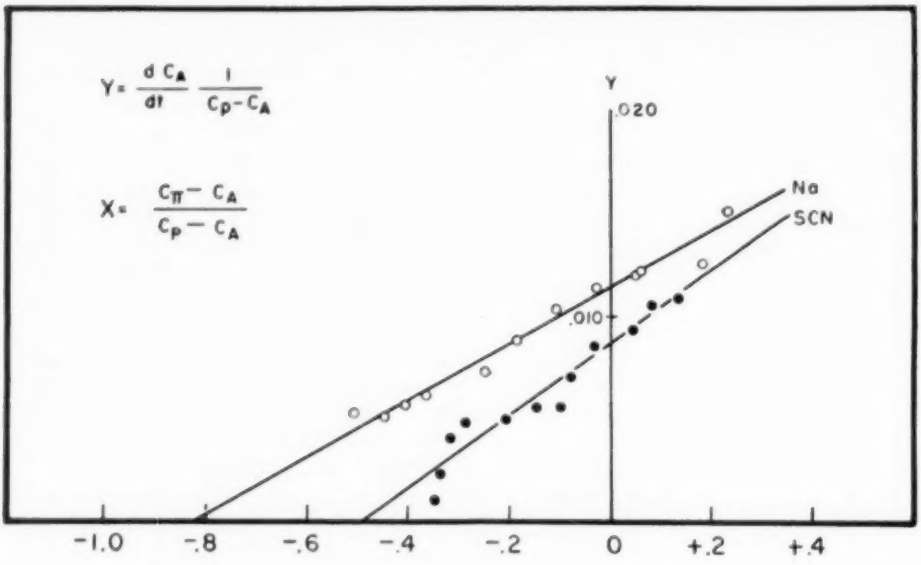



Fig. 1.—Linear plot as a test of the validity of applying the Kinsey-Palm differential equation to their experimental data. The intercepts on the $Y$ axis give estimates of $K_d$; the slopes of the lines give estimates of $K_f$.

centration. Successive calculated curves are produced with successive test values of $K_f$ and $K_d$, and those test values are chosen which yield a calculated curve in best agreement with the experimental data.

In the procedure which we have outlined, $\frac{dC_a}{dt}$ is estimated directly from the smoothed curve which fits the experimental data. Using this estimate in Equation (2) enables the selection of the "best value" of $K_f$ and $K_d$ by graphical procedures equivalent to least-squares calculations.

It will be seen, then, that the experimental results of Kinsey and Palm do, in fact, fit with reasonable approximation to Equation (1), but what are the assumptions that are made in saying that Equation (1) applies? The fact that Equation (1) fits does not prove that all other considerations are negligible. Now we shall attempt to analyze the quantitative role of some of the aspects omitted from consideration in formulating Equation (1). The assumptions involved in applying Equation (1) to the experimental data are (*a*) that the test substance is not metabolized within the eye; (*b*) that the posterior chamber provides a fair sample of fluid momentarily passing through the pupil; (*c*) that exchange of test substance between anterior chamber and cornea is negligible; (*d*) that outflow from the anterior chamber is in bulk, i. e., without ultrafiltration; (*e*) that the posterior chamber tap provides a sample of fluid uncontaminated by anterior chamber aqueous or by vitreous, and (*f*) that no significant fluid volume enters the anterior chamber except via the pupil. The first of these assumptions is obviously satisfied by the test substances which Kinsey and Palm used. Each of the remaining assumptions requires detailed analysis.

2. Stream-Lined Flow Through the Posterior Chamber

If there were perfect continuous mixing of the posterior chamber fluid, then a sample of this fluid would constitute an exact sample of the fluid momentarily passing through the pupil. The slow flow of fluid through the posterior chamber, however, precludes any appreciable mixing by turbulence. Thermal convection within the posterior chamber must be negligibly small. The elaborate baffles provided by the ciliary processes and by the zonule would seem to insure streamline flow. Under these circumstances the only appreciable mixing in the posterior chamber must be by diffusion from one streamline to the next.

If there is streamline flow through the posterior chamber, there should be a lag period between the presentation of a test substance in the blood and its appearance in the pupil. During this lag period the test substance should be demonstrable in the posterior chamber. In experiments with Linnér, to be published elsewhere, this has been found to be true. With fluorescein as the test substance, a lag period of 60-80 seconds was observed with respect to appearance in the pupil, while at 20-30 seconds after intravenous injection the dye could be recovered in the posterior chamber.

The mathematical analysis of the problem is difficult, since the geometrical form of the posterior chamber is very complex. One can approach the analysis by considering the posterior chamber successively (1) as a simple cylindrical tube, (2) as a right cylindrical annulus, (3) as an annulus the inflow surface of which is a cone such that streamlines from inlet to outlet are of varying length, (4) as an annulus of this form the inflow surface of which is corrugated, etc. For the first two hypotheses a full mathematical solution can be obtained. For the more complex hypotheses we have been able to reach only approximations. On the simplified Models (1) and (2), it is found that during the first few moments a mixed sample from the posterior chamber must give a very bad estimate of what is simultaneously passing through the pupil, but that after a time interval equal to five times the lag period the concentration in a mixed sample from the posterior chamber should differ from that simultaneously passing through the pupil by no more than 4%. The disparity becomes smaller the longer the experiment is continued.

To proceed from these simplified models to the complex structure of the actual posterior chamber involves the introduction into the model of variability in the lengths of streamlines, and of the complex intermingling of long and short streamlines. Variability in length of streamlines and the intermingling of long and short streamlines is a characteristic of turbulence. It seems likely, therefore, that actual events in the rabbit's posterior chamber will show less deviation from perfect mixing than is predicted on the basis of the simplified models. That this conclusion is at least partially true may be seen as follows:

Copeland and Kinsey [7] have estimated the volume of the posterior chamber in rabbits as approximately one-fifth that of the anterior chamber. From some experiments to be reported elsewhere this would appear to be a slight underestimate, the true value being about one-third that of the anterior chamber. At any rate, the filling time for the posterior chamber, i. e., the time required for the inflow of a volume equal to that of the posterior chamber, would be about 10-15 minutes. Now, on the basis of the simplified Models (1) and (2) given above, the lag period would be one-half or two-thirds the filling time. The actual lag period is only slightly more than one minute, indicating that some of the streamlines are short and swift, as in partial mixing.

It would seem appropriate to conclude that the posterior chamber samples early in the experiment are not fully representative of the fluid contemporaneously passing through the pupil. As the experiment progresses, errors from this source diminish. It was, in part, for this reason that in estimating $K_f$ in the preceding section of this paper, data from Kinsey and Palm on experiments shorter than 30 minutes were omitted.‡

It should be pointed out that when a sample of fluid is withdrawn from the posterior chamber, the valleys between the ciliary processes are not obliterated. Thus, the most recently secreted fluid lying, in part, in those valleys is not fully represented in the sample taken, and the sample probably represents the fluid contemporaneously passing through the pupil somewhat better than would a theoretically correctly mixed sample.

### 3. The Cornea as a Reservoir in Exchange with the Anterior Chamber

Equation (1) does not take into account any possible exchange between anterior chamber and cornea. If we wish to take account of such possible exchange, the equation must be rewritten

$$\frac{dC_a}{dt} = K_f(C_\pi - C_a) + K_d(C_p - C_a) + K_{dc}(C_c - C_a) \qquad (4)$$

in which $K_{dc}$ represents the diffusion coefficient for exchanges between anterior chamber and cornea (expressed in terms of anterior chamber concentration change) and $C_c$ the concentration of the test substance within the cornea.

Maurice [8] has reported experiments in which the concentration of isotopically labeled sodium in cornea, anterior chamber, and plasma was recorded following intravenous injection and other modes of administration of this test substance. From his data, $K_{dc}$ $(C_c - C_a)$ can be estimated at appropriate time intervals. Equation (4) may be rewritten for comparison with Equation (2) as follows:

$$\frac{dC_a}{(C_p - C_a)dt} - K_{dc}\frac{C_c - C_a}{C_p - C_a} = K_f\frac{C_\pi - C_a}{C_p - C_a} + K_d \qquad (5)$$

The right-hand side of Equation (5) is identical with the right-hand side of Equation (2). If we call the left-hand side of Equation (5) $Y''$, we may plot $Y''$ vs. $X$ just as we have previously plotted $Y$ vs. $X$. As a matter of fact, $Y''$ will differ from $Y$ by a small correction, equal to $-K_{dc}\cdot\frac{C_c - C_a}{C_p - C_a}$. Since $C_a$ is, in general, larger than $C_c$, but smaller than $C_p$, this correction, in general, will be positive. Maurice estimates it to be roughly 10% to 15% of $Y$. The net result of applying this correction is, therefore, to increase the estimate of $K_f$ and $K_d$ each by 10% to 15%. This would seem to be quite reasonable, since the volume of the cornea is about 25% of that of the anterior chamber and the 10% to 15% correction figure is equivalent to assuming that about one-half of the corneal exchange of test substance is with the anterior chamber, and that the cornea achieves a final concentration comparable to that in the anterior chamber. Evidence that this is so, with respect to sodium, may be derived from Maurice's data.

Without the experimental determination of the time course of corneal concentrations of other test substances, the corresponding corrections cannot be computed. However, unless the final concentration in the cornea is higher than that in the anterior chamber, corrections larger than 10% to 15% are unlikely.

‡ In data to be published separately, it will be shown that under favorable conditions the linear relations expressed in Equation (2) are conformed to by data withdrawn as early as five minutes after the beginning of the experiment.

If we incorporate a 10% to 15% upward correction into the value of $K_f$, already estimated at 0.0155, we obtain an estimate of 0.017 to 0.018.

### 4. Outflow in Bulk

An assumption underlying the formulation of Equation (1) is that, so far as it concerns the test substances to which this equation is applied, outflow is in bulk; i. e., the concentration of the test substance in the efflux is the same as that momentarily present in the anterior chamber. The alternative possibility for consideration is that outflow might be by ultrafiltration, the concentration in the efflux being less than that in the chamber.

Ultrafiltration requires energy, and only 10-15 mm. Hg pressure is available to provide energy. For an ion, such as sodium, present in high concentration in the aqueous the available energy would not suffice to diminish the concentration in the efflux by as much as 1%. The outflow must, therefore, be substantially in bulk so far as concerns sodium. For other test substances the experimental concentrations used may be so low that this argument does not necessarily hold.

It is of interest to see how Equation (1) would be altered by assuming ultrafiltration to occur. Under such circumstances the outflow concentration would be $nC_a$, where $n$ is some fraction less than unity.

$$\frac{dC_a}{dt}=K_f(C_\nu-nC_a)+K_d(C_p-C_a) \tag{6}$$

If Equation (6) is divided by $(C_p-C_a)$, we obtain

$$\frac{dC_a}{(C_p-C_a)dt}=K_f\frac{C_\nu-nC_a}{C_p-C_a}+K_d \tag{7}$$

If the hypothesis of ultrafiltration at the outflow is correct, a plot of $\frac{dC_a}{(C_p-C_a)dt}$ versus $\frac{C_\nu-nC_a}{C_p-C_a}$ should fall on a straight line. We have already shown that for $n=1$ the plot is substantially linear. Our test, then, consists in finding whether other values of $n$ yield plots which deviate significantly from linearity. It is readily found that with thiocyanate as test substance the hypothesis that $n$ is 0.9 or less yields recognizably nonlinear plots. Consequently, outflow for this test substance is likewise substantially in bulk.

### 5. Reliability of the Posterior Chamber Sample

Kinsey § has discussed in considerable detail the question of the possible contamination of the posterior chamber samples by anterior chamber fluid. The evidence seems very good that such contaminations are avoidable in a properly performed posterior chamber tap. Contamination by vitreous fluid is less readily excluded. The insertion of the needle necessarily ruptures the anterior hyaloid and zonular boundaries. We have found that with sufficient patience appreciable volumes of fluid can be obtained directly from the vitreous cavity even with a fine needle. If, in attempting to obtain posterior chamber fluid, the tapping needle is twisted and turned, very large samples of fluid may be withdrawn, samples several times as large as any reasonable estimate of the total volume of the posterior chamber. Such large samples, if taken early in the course of the experiment, contain concentrations of the test substance lower than those concurrently found in either chamber or plasma and comparable to those obtained by direct vitreous taps. It is, therefore, possible to contaminate the posterior chamber sample with vitreous. The chief safeguard against this is awareness of the hazard and care to enter the posterior chamber by a direct puncture, rotating the needle on its axis if necessary, but not

§ References 1 and 3.

shifting the axis during the whole procedure. At a later stage in our argument it will be possible to show that there is intrinsic evidence in the data of Kinsey and Palm making it unlikely that any significant vitreous contamination entered into their posterior chamber taps.

### 6. Fluid Transfer Across the Iris

The aqueous is hypertonic with respect to plasma,[2] and the blood-aqueous barrier of the anterior chamber is permeable to water.[9] It follows that some water must be transferred osmotically from plasma to anterior chamber. Equation (1) takes no account of this diluting procedure. The question is whether this effect is, in fact, negligibly small. At first sight, the osmotic water movement might be expected to be appreciable, for the permeability of biological boundaries to water in general exceeds their permeability to solutes, and, with respect to some solutes, diffusional exchange contributes an appreciable fraction of the anterior chamber turnover.

Kinsey has found that the posterior chamber aqueous is hypertonic with respect to anterior chamber aqueous by not more than 1%. It follows that the aqueous in its passage through the anterior chamber is diluted osmotically by not more than 1%. Any such dilution would consist, in part, in the diffusion outward of solutes and, in part, in the inward osmotic transfer of water. The relative velocities of these two processes would be determined by the relative permeability of the barrier to water *vs.* solutes, and this can be estimated only very roughly from the available data. However, even if all the dilution were water import, the net rate of osmotic inflow would be no more than 1% of the flow from posterior chamber, for the aqueous is diluted by no more than this factor in its passage through the anterior chamber. This is not to say that if one labeled the water molecules in the anterior chamber, one might not find them exchanging with plasma water at a very rapid rate. However, what we are concerned with here is not turnover rate but net transfer. The turnover rate of water is effected by the diffusional force of the total concentration of water, i. e., some 55 osmoles per liter. The net osmotic transfer is effected by osmotic excess of aqueous versus plasma, i. e., some 0.006 osmole per liter. The ratio of these forces is of the order of $10^4$.

This discussion can be put into more precise terms if we rewrite Equation (1) so as to include the osmotic dilution of anterior chamber aqueous

$$\frac{dC_a}{dt} = K_f(C_w - C_a) + K_d(C_p - C_a) - K_w C_a \qquad (8)$$

in which $K_w$ is the rate per minute at which the aqueous is being diluted. Since this rate can be no more than 1% of the rate of flow, and since the rate of flow, $K_f$, is approximately 0.017, it follows that a maximal estimate for $K_w$ is roughly 0.0002. Kinsey and associates,[9] using heavy water as test substance, found the turnover in the anterior chamber to be characterized by a rate coefficient of about 0.2 (half-life of three minutes). This is perhaps an underestimate of the turnover rate of water, since mixing in the anterior chamber might become a serious bottleneck under these conditions. The osmotic transfer is operated by a force $10^{-4}$ times that operating the turnover. Hence a minimal estimate for the osmotic transport rate is $2\times10^{-5}$. The true value of $K_w$, therefore, lies between $2\times10^{-5}$ and $2\times10^{-4}$. This small rate of dilution can be neglected with impunity in the analysis of aqueous humor dynamics.

Up to the present we have considered water transfer from iris vessels to anterior chamber by osmotic forces. The conclusion that the rate of such osmotic transfer is negligibly small would not, at first sight, appear to exclude simple

hydrostatic ultrafiltration of fluid through the iris capillaries. The available pressure head for such ultrafiltration is the capillary blood pressure minus the intraocular pressure minus the protein osmotic pressure of the plasma. No exact estimate for this pressure head can be given, but it cannot be more than a few millimeters of mercury and may, in fact, be negative. When we compare this with the osmotic pressure excess of 100 mm. Hg, which we have already shown to be ineffective across this same boundary, we must conclude that under normal conditions the contribution of ultrafiltration from the iris capillaries is also negligible. With inflammation and other reactive changes in the iris vessels this would, of course, no longer be true.

## PART II

### I. Posterior Chamber Dynamics

In preceding sections it has been shown that the differential Equation (1) used by Kinsey and Palm for the analysis of their results is valid within rather wide limits and that the coefficients of flow and diffusion which they have calculated are reliable within the limits of accuracy of the experiment. It would be of great advantage if Equation (1) could be manipulated in such a way as to eliminate $C_\pi$ (the posterior chamber concentration) so as to reveal what information, if any, can be obtained from knowledge of anterior chamber and plasma concentrations alone. All of the older experiments present only data of this latter type, and, if we wish to compare these older data of this latter type, and if we wish to compare these older data with those including posterior chamber taps, a mathematical framework is required for such comparison.

The argument that follows is necessarily a complex one, and it may assist the reader to outline in advance the course it will take and why. What we want is an equation expressing the course of the concentration in the anterior chamber ($C_a$) as a function of time ($t$). Equation (1) tells us explicitly only about the rate of change of concentration in the anterior chamber. It is the differential equation whose integral we seek.

Equation (1) contains $C_\pi$ as an independent variable, and before we can integrate Equation (1), we must obtain an expression for $C_\pi$ as a function of time. To do this, we start by writing a differential Equation (9) for the posterior chamber which expresses our best intuitions as to how the test substance gets into and out of the posterior chamber. Since there must be diffusional exchange between posterior chamber and lens and vitreous, the concentrations in these structures enter as independent variables into Equation (9). For the sake of simplicity, we have lumped together vitreous and lens as if they constituted a single reservoir and have designated the concentration in that reservoir as $C_r$.

Just as Equation (1) cannot be solved without an explicit equation for $C_\pi$, so Equation (9) also cannot be solved without an explicit expression for $C_r$. Again, calling on our physiological intuition, we write a differential equation for the reservoir.[9] Evidently, the reservoir must be in diffusional exchange only with plasma and posterior chamber. Equation (10), therefore, introduces no new independent variable. We have reached the end of writing new equations and can apply to the set (1), (9), and (10) standard mathematical procedures leading to the solution we desire. We obtain, in fact, explicit equations for $C_a$, $C_\pi$, and $C_r$, each as a function of time. Each of these equations can, in turn, be compared with the experimental data. These equations are multiple exponential equations, and conventional graphical procedures are available to test their fit with the experi-

mental data. In reaching these equations, it is convenient to introduce some new constants. It is, however, possible to define these new constants in terms of the diffusion and flow coefficients that are themselves defined in Equations (1), (9), and (10), plus the boundary conditions of the integration, which in this case are the initial and final (steady-state) concentrations in anterior chamber, posterior chamber, and reservoir.

All of this is done with the assumption that the plasma concentration remains constant during the experiment. Various other simplifying assumptions will be noted as the argument is developed. With this outline of the prospective argument in mind, we return to that argument in detail.

As noted above, Equation (1) contains $C_{\pi}$ as an independent variable. In order to eliminate this variable, we start with an approximate differential equation for the posterior chamber.

Kinsey and Palm have suggested two forms for the posterior chamber differential equation, depending on whether the test substance enters by secretion (i. e., at a fixed concentration relative to plasma) or by diffusion (i. e., at a rate proportional to the concentration difference between plasma and posterior chamber). For the purpose of the present discussion these two equations will be fused into one.

$$\frac{dC_{\pi}}{dt}=K_{f_{\pi}}(C_s-C_{\pi})+K_{d_{\pi}}(C_p-C_{\pi})+K_{d_{\pi}}'(C_r-C_{\pi}) \qquad (9)$$

In this equation, $K_{f_{\pi}}$ represents the rate of flow per minute as a fraction of posterior chamber volume; $K_{d_{\pi}}$, the diffusion coefficient between plasma and posterior chamber, and $K_{d_{\pi}}'$ the diffusion coefficient between the posterior chamber and the adjacent reservoir (vitreous and lens). If $K_{d_{\pi}}$ is zero, this equation becomes essentially identical with the Kinsey-Palm secretion equation; if $C_s$ is zero, it becomes identical with their diffusion equation. $C_r$ is the concentration in the environmental reservoir. $C_s$ may be defined as the concentration "secreted," or, more precisely, it is the concentration which would be reached in the posterior chamber at steady state if there were no diffusional gains or losses, i. e., if $K_{d_{\pi}}$ and $K_{d_{\pi}}'$ were zero.

Kinsey and Palm were fully aware of the simplifying assumptions involved in the formulation of their equations. The environmental reservoir, with which the posterior chamber is presumed to be in diffusional exchange, is, for purposes of simplification, assumed to be a single, well-mixed chamber characterized by a single-lumped diffusion coefficient. The posterior chamber itself is also assumed to be well mixed. The justification for the use of these simplifying assumptions by Kinsey and Palm and by us is that they make the mathematics manageable and that, as will be apparent later, they fit the experimental data with reasonable approximation.

In Equation (9), $C_r$, the concentration in the environmental reservoir, is an independent variable. Without any additional assumptions except that the reservoir is in diffusional exchange with both posterior chamber and plasma, one obtains a differential equation for the reservoir:

$$\frac{dC_r}{dt}=K_r'(C_{\pi}-C_r)+K_r''(C_p-C_r) \qquad (10)$$

where $K_r'$ and $K_r''$ are, respectively, the diffusion constants for exchanges between reservoir and posterior chamber and between reservoir and plasma, expressed in terms of reservoir concentrations.

In order to eliminate $C_r$ and $\frac{dC_r}{dt}$ from Equations (9) and (10), a third equation is required. This is obtained by differentiating Equation (9) with respect to time, assuming $C_p$ to be constant.‖

$$\frac{d^2C_\pi}{dt^2}=K_{a_\pi}'\frac{dC_r}{dt}-(K_{t_\pi}+K_{a_\pi}+K_{a_\pi}')\frac{dC_\pi}{dt} \tag{11}$$

Eliminating $C_r$ and $\frac{dC_r}{dt}$ from Equations (9), (10), and (11) and writing $K_\pi$ for $(K_{t_\pi}+K_{a_\pi}+K_{a_\pi}')$, and $K_r$ for $(K_r'+K_r'')$, we obtain

$$\frac{d^2C_\pi}{dt^2}+(K_r+K_\pi)\frac{dC_\pi}{dt}+(K_rK_\pi-K_{a_\pi}K_r')C_\pi=\text{constant} \tag{12}$$

This equation is integrable and yields as its solution the double exponential

$$C_\pi=C_{\pi_\infty}[1-Me^{-K_1t}-(1-M)e^{-K_2t}] \tag{13}$$

where $C_{\pi_\infty}$ is the steady-state concentration in the posterior chamber.

$$K_1=\frac{K_\pi+K_r}{2}+\tfrac{1}{2}\sqrt{(K_\pi-K_r)^2+4K_{a_\pi}'K_r'} \tag{14}$$

$$K_2=\frac{K_\pi+K_r}{2}-\tfrac{1}{2}\sqrt{(K_\pi-K_r)^2+4K_{a_\pi}'K_r'}$$

$M$ is a constant whose value can be determined by differentiating Equation (13) with respect to $t$ and determining the rate of change of $C_\pi$ at $t=0$.

$$\left[\frac{dC_\pi}{dt}\right]_{t=0}=C_{\pi_\infty}[MK_1+(1-M)K_2] \tag{15}$$

From Equation (9) we have

$$\left[\frac{dC_\pi}{dt}\right]_{t=0}=K_{t_\pi}C_a+K_{a_\pi}C_p \tag{16}$$

Combining Equations (15) and (16) we obtain

$$M=\frac{K_{t_\pi}C_a+K_{a_\pi}C_p-K_2C_{\pi_\infty}}{C_{\pi_\infty}(K_1-K_2)} \tag{17}$$

The steady-state value $C_{\pi_\infty}$ can also be defined in terms of Equation (9). At the steady state the rate of change is zero, and we have

$$K_{t_\pi}C_a+K_{a_\pi}C_p+K_{a_\pi}C_{r_\infty}=K_\pi C_{\pi_\infty} \tag{18}$$

Moreover, the steady-state value of the reservoir can be obtained in a similar way from Equation (10)

$$K_r'C_{\pi_\infty}+K_r''C_p=K_rC_{r_\infty} \tag{19}$$

Thus, all the constants in Equation (13) are defined in terms of the constants in Equations (9) and (10). Moreover, Equation (18) makes it possible to evaluate $C_a$ in terms of the diffusion and flow constants and the steady-state concentrations.

The two exponents $K_1$ and $K_2$ of the double exponential Equation (13) are defined by rather complicated Equations (14), which obscures their physical meaning. However, from Equation (14) it can be seen that if $K_{a_\pi}'$ and $K_r'$ (both of which define the diffusional exchange between posterior chamber and reservoir) are sufficiently small, then $K_1=K_\pi$ and $K_2=K_r$. Thus, $K_1$ is approximately the turnover rate of the test substance in the posterior chamber, while $K_2$ is the turnover rate in the posterior reservoir. In order to define the latter more exactly,

‖ If $C_p$ varies during the course of the experiment, $C_a$ may also vary, possibly in simple proportion to $C_p$. If an explicit equation for the variation of $C_p$ with time is available, the differential equations may still be integrable, but this will add greatly to the mathematical complexities without adding much to the information. For most substances, following a single intravenous injection, the plasma time course can be described by a single or multiple exponential equation. However, the graphical exponential analysis of the associated concentration course in the anterior and posterior chambers will not reveal these additional exponents unless they differ significantly in magnitude from those characteristic of experiments with constant plasma concentration.

it will be convenient to obtain an equation for $C_r$ in terms of $t$. This can be done by substituting Equation (13) and its first derivative with respect to time into Equation (9) and solving for $C_r$.

$$C_r = C_{r_\infty}[1 - Ne^{-K_1 t} - (1-N)e^{-K_2 t}] \P \tag{20}$$

where

$$C_{r_\infty} = \frac{K_\pi C_{\pi_\infty} - K_{1_\pi} C_a - K_{4_\pi} C_v}{K_{4_\pi}} \tag{21}$$

$$N = M \frac{(K_\pi - K_1) C_{\pi_\infty}}{K_{4_\pi} C_{r_\infty}}$$

In general, $N$ turns out to be a small negative number, and $K_1$ contributes a small initial lag in the concentration time course of the reservoir. Thus, $K_2$ represents the filling rate of the reservoir after a small initial lag. Kinsey and Palm reached a similar conclusion in their less detailed analysis of the posterior chamber dynamics.

¶ Dr. Erik Palm points out that the exponents $K_1$ and $K_2$ occupy similar positions in the explicit equation for $C_r$ as they do in the equation for $C_\pi$.

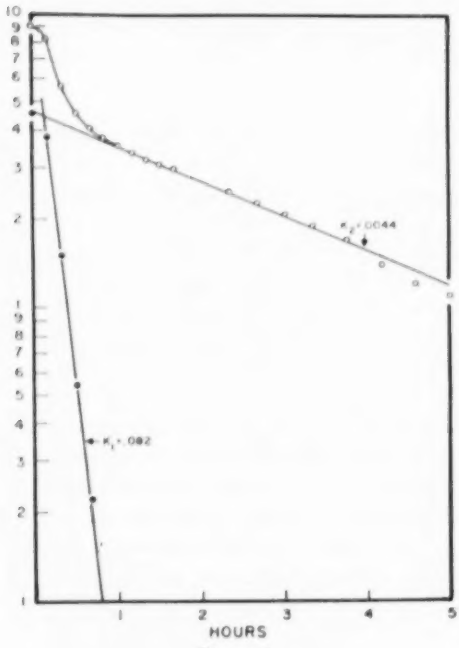



Figure 2

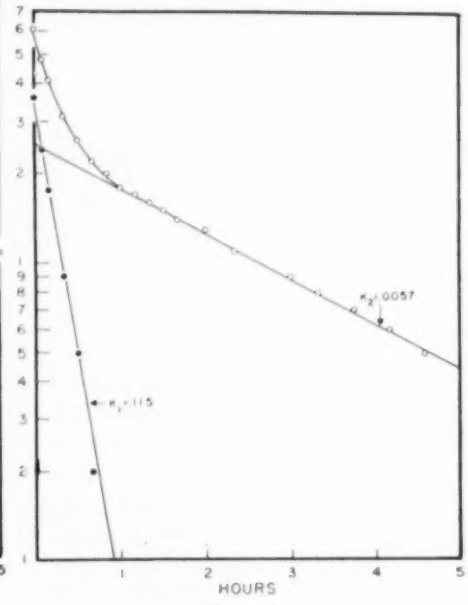



Figure 3

Fig. 2.—Graphical exponential analysis of Kinsey and Palm's data for radioactive sodium in the posterior chamber. The open circles represent a plot of log $(C_{\pi_\infty} - C_\pi)$ *vs.* time. A value of 0.92 is chosen for $C_{\pi_\infty}$, since this was the experimentally determined value at 24 hours after injection of the test dose. Using this figure omits consideration of an additional, very slow component, which is visible only in experiments lasting several days. A straight line is fitted to the tail of the open-circle data. The values indicated by this straight line in the early portions of the experiment are subtracted from the open-circle data, yielding the solid-circle data. The latter are satisfactorily fitted by another straight line, indicating that the experimental data conform approximately to a double exponential equation. The slopes of the two lines are measures of the two exponents $K_1$ and $K_2$ of such an exponential equation.

Fig. 3.—Graphical exponential analysis of Kinsey and Palm's data for thiocyanate in the posterior chamber. The treatment is the same as in Figure 2.

These equations do not invite too precise an interpretation, since in actual practice the reservoir-filling coefficient, $K_2$, is a lumped coefficient representative of several chambers (vitreous and lens) and the experimental estimate of $K_2$ will be somewhat influenced by the segment of the semilog plot used for this estimation. Similarly, the experimental estimate of the turnover rate in the posterior chamber, $K_1$, is blurred by the fact that no allowances have been made for the initial rapid rise of the plasma concentration. Nevertheless, our present purpose is precisely to determine whether or not these simplified equations do give an approximate description of the experimental events in the posterior chamber.

As the first step toward testing the empirical validity of Equation (13), we can inquire whether the posterior chamber data of Kinsey and Palm conform to this equation. Using the conventional method of graphical analysis, we have plotted log $(C_{\pi\infty} - C_\pi)$ vs. $t$. The results are shown in Figures 2 and 3. Substantially good fits are obtained. The following values of the coefficients of Equation (13) for the two test substances studied may be tabulated.

It would appear that the values of $K_2$ are reasonably well established by this analysis. The estimates of $K_1$ are less certain, since no allowance has been made in these calculations for the fact that the plasma concentrations are rapidly rising during the first 10-20 minutes of the experiment. In spite of this unresolved

TABLE 2.—*Values of Coefficients of Equation (13) for Sodium and Thiocyanate*

| Test Substance | $M$ | $K_1$ | $K_2$ |
|---|---|---|---|
| $Na^+$ | 0.50 | 0.09 | 0.0044 |
| Thiocyanate | 0.57 | 0.115 | 0.0057 |

aspect of the problem, there is no question that the double exponential equation as formulated (Equation 13) furnishes a very good empirical description of the course of concentration change in the posterior chamber.

In order to study this matter further, it has seemed desirable to obtain data concerning the concentration of at least one test substance in the vitreous. In a series of rabbits, 100$\mu$c of radioactive $Na^{24+}$ as chloride in isotonic saline solution were injected intraperitoneally. Plasma, posterior chamber, anterior chamber, and vitreous samples were removed at chosen times. The samples were weighed, placed in small metal pillboxes previously moistened with a solution of detergent, made up to 1 cc. with distilled water, evaporated to dryness, and their activity counted, using a thin window counter. No correction for internal adsorption within the sample was found necessary. The anterior, posterior, and plasma samples showed a time course in relation to the experiment in essential agreement with the findings reported by Kinsey and Palm.

The vitreous samples were obtained with a #18-gauge needle inserted through the sclera at the equator and directed so that the point of the needle could easily be observed lying behind the posterior pole of the lens. Aspiration supplemented by moderate pressure on the sclera enabled the obtaining of taps 0.5 to 1.0 cc. in volume. From these large samples duplicate aliquots were used for counting. In view of the large volume, sufficiently high counts were obtained even on samples drawn as soon as 20 minutes after the intraperitoneal injection of the test solution. The radioactivity per gram of vitreous fluid was recorded as per cent of the simultaneously determined activity per gram of water in the plasma (95.4% of

plasma weight). The data are shown in Figure 4, using 103% of plasma as an estimate of the steady-state value $C_{v\infty}$. Each point on the curve represents the average of four or more eyes. In all, samples were obtained from 33 eyes. The series was terminated with only this relatively small number of observations, because the agreement between paired observations was so good and the data plotted onto such a smooth curve that further experiments seemed unnecessary.

The time course of the concentrations found in the vitreous is well described by a single exponential with a small initial lag, as was to be expected from Equations (20) and (21). The exponent which characterizes the rate of filling of the vitreous is a good deal smaller ($K_v$=0.0015) than that which describes the tail of the posterior chamber curve ($K_2$=0.0044). It should be remembered, how-

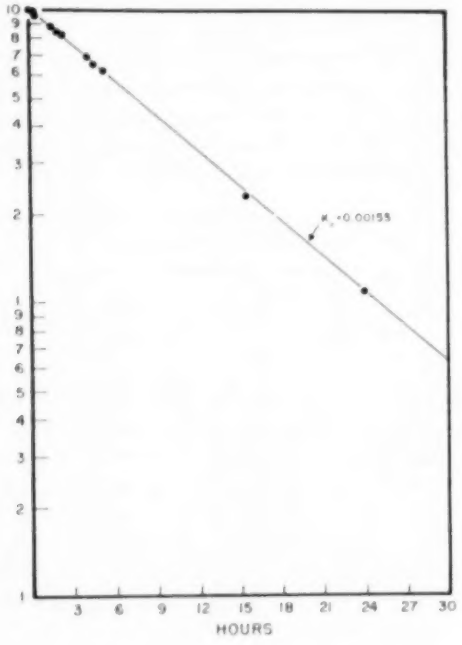



Fig. 4.—Graphical exponential analysis of our data for radioactive sodium in the vitreous following a simple intraperitoneal injection of 100 mc. of $Na^{+24}$ as NaCl. The data conform to a single exponential equation after a small initial lag.

ever, that $K_2$ is the lumped exponent describing in one average figure the filling of the several compartments of the posterior reservoir. $K_v$, on the other hand, describes a single one of these compartments. Moreover, $K_2$ is determined experimentally mainly by the earlier part of the experiment and consequently represents, so to speak, the turnover rate of that part of the posterior reservoir that is closest to the posterior chamber.

### 2. Anterior Chamber Dynamics

The foregoing analysis has made it clear that the double exponential Equation (13) gives a fairly satisfactory representation of the course of concentration change

in the posterior chamber. If we insert the value of $C_\pi$ given by Equation (13) into Equation (1), we have

$$\frac{dC_a}{dt}=K_f C_{\pi_\infty}[1-Me^{-K_1 t}-(1-M)e^{-K_2 t}]+K_d C_p-(K_f+K_d)C_a \qquad (22)$$

On integration, assuming $C_p$ to be constant, we obtain

$$C_a=C_{a_\infty}[1+Ke^{-K_1 t}-Se^{-K_2 t}-(1+R-S)e^{-K_o t}] \qquad (23)$$

where $K_o=K_d+K_f$ ($K_o$ is $K_{out}$ in the earlier notation of Kinsey and others).

$$K=\frac{K_f C_{\pi_\infty} M}{C_{a_\infty}(K_1-K_o)} \qquad S=\frac{K_f C_{\pi_\infty}(1-M)}{C_{a_\infty}(K_o-K_2)} \qquad (24)$$

The applicability of this equation to anterior chamber data may be tested by the usual graphical analysis. We wish to know the following: 1. Do the data conform to a triple exponential? 2. Do we obtain estimates of $K_2$ which agree with those obtained from the analysis of posterior chamber data? 3. Do we obtain an estimate of $K_o$ in agreement with our estimates of $K_f+K_d$ obtained from application of Equation (1) to both anterior and posterior chamber data taken together? We shall not expect exact agreement between the estimates of $K_1$ from anterior and posterior chamber data separately, since, owing to streamline flow in the posterior chamber, the concentrations found in the posterior chamber in the early parts of the experiment do not represent properly the concentrations in fluid simultaneously passing through the pupil.

Table 3 gives the comparisons of the relevant data.

TABLE 3.—*Summary of Constants for Sodium and Thiocyanate*

| Test Substance | (1) Posterior Chamber | | (2) Anterior Chamber | | (3) Anterior Chamber Corrected | | (4) | (5) |
|---|---|---|---|---|---|---|---|---|
| | $K_1$ | $K_2$ | $K_2$ | $K_o$ | $K_1$ | $K_o$ | Kinsey & Palm, $K_o$ | $X$ vs. $Y$ Plot, $K_o$ |
| Na | 0.09 | 0.0044 | 0.0033 | 0.031 | 0.08 | 0.027 | 0.030 | 0.026 |
| SCN | 0.115 | 0.0057 | 0.0054 | 0.026 | 0.09 | 0.027 | 0.027 | 0.026 |

The graphical analysis of the anterior chamber data has been performed in two ways. In the first place, the anterior chamber data have been treated independent of similar graphical exponential analysis of the posterior chamber data. The results provide estimates of $K_2$ and $K_o$ given in Columns (2) of Table 3. It will be seen that the estimates of $K_2$ from the anterior chamber are in fair agreement with those from the posterior chamber, Column (1). Actually, the posterior chamber estimate of $K_2$ should be much more reliable, since the tail of the semilog plot of the posterior chamber data tends to be linear over a much longer portion of the experimental time interval (Figs. 2 and 3). Consequently, we have redrawn the graphical analysis of the anterior chamber data using the posterior chamber estimate of $K_2$ for the tail (Figs. 5 and 6). This gives the estimates of $K_1$ and $K_o$ shown in Columns (3) of Table 3.

The agreement of the estimates in Table 3 is remarkably good and makes it clear that approximate estimates of $K_o$ can be obtained by the exponential analysis of anterior chamber data through the application of Equation (23).# Previous

# The good agreement between the estimate of $K_o$ from a consideration of the anterior chamber and plasma data alone, with the estimates of $K_f+K_d$ derived from application of Equation (1) to data, including those derived from the posterior chamber, enables us to give an answer to the question raised in Section V of Part I, above. In that section the possibility of contamination of the posterior sample with vitreous was noted. If there were a gross contamination of this sort, the inclusion of such data should lead to serious errors in the estimates. The good agreement of the estimates makes such contamination unlikely.

workers in this field have indeed attempted to estimate $K_o$ from anterior chamber data, but, because they were unaware of the large influence of the reservoir factor ($K_2$), serious underestimation of $K_o$ has resulted.

As an illustration of the effect of omitting consideration of the reservoir factor, the thoughtful and extensive studies of Davson* may be mentioned. Davson reports on experiments in which the plasma levels of a variety of test substances were kept constant for periods of two to three hours following the initial injections. Since the experiments were terminated after this relatively short period, true steady-state values for $\frac{C_{a\infty}}{C_p}$ could not be obtained directly. Davson applied graphical exponential analysis to the truncated data and estimated the steady-state concentration by finding out what value assigned to $C_{a\infty}$ would render the tail of his

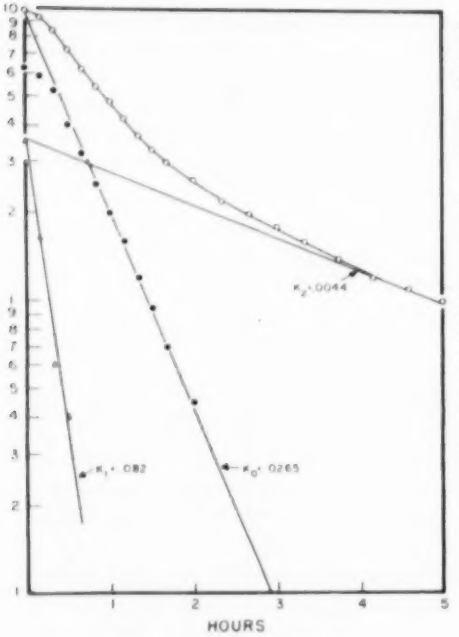



Figure 5

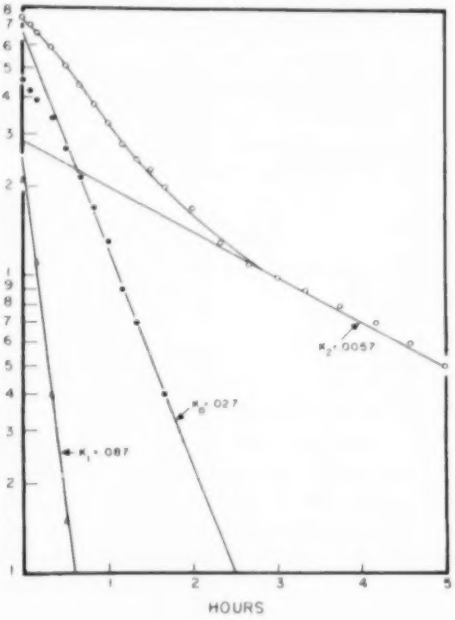



Figure 6

Fig. 5.—Graphical exponential analysis of Kinsey and Palm's data for radioactive sodium in the anterior chamber, showing that these data conform to a triple exponential equation.

Fig. 6.—Graphical exponential analysis of Kinsey and Palm's data for thiocyanate in the anterior chamber, showing that these data conform to a triple exponential equation.

exponential plot a straight line. He took the slope of this straight line as a basis for estimating $K_o$. If we apply this method of analysis to Kinsey's data, we obtain for $Na^+$ and thiocyanate, respectively, 0.015 and 0.017 as estimates of $K_o$, estimates which are 35%-50% too low.

As a matter of fact, in Kinsey and Grant's original attack on aqueous humor dynamics, not only the reservoir factor but also the initial lag period (illustrated in Figures 5 and 6 by the upward convexity of the curve in the initial 10-20 minutes) was largely disregarded. In this early study a complicated graphical method was

* References 10 and 11.

used to estimate $K_a$, in view of large statistical variations in the data. It is not easy to apply this method to Kinsey and Palm's present data, but that early method amounted in essence to an estimate of the $K_a$ on the assumption that a simple exponential equation was applicable to the data. On examining Figures 5 and 6, it is seen that the anterior chamber has reached half its steady-state value in 57 and 52 minutes, respectively. If a simple exponential equation were supposed to hold, this would lead to estimates of $K_a$=0.012 and 0.013 for $Na^+$ and $SCN^-$, respectively.

Kinsey and Grant, in their earlier study,[5] assumed that $K_f$ must be the same for all substrates and that for the substrate showing the smallest value of $K_a$, $K_d$, the diffusional exchange between plasma and aqueous, was negligibly small. Thus, they reached an estimate of 0.010 to 0.012 for $K_f$. Though this earlier estimate is now shown to be too small, the achievement of this first approximation represented an important forward step at the time. As a matter of fact, the weight of the argument in Kinsey and Grant's early publication was not on the validity of the first approximate estimate of $K_f$, but on the demonstration that an actual through-and-through flow of aqueous occurs, i. e., the demonstration that $K_f$ has some value greater than zero.

## SUMMARY AND CONCLUSIONS

An analysis of the recent study by Kinsey and Palm[4] shows that there are wide limits within which the differential equations which they have used in the analysis of their data may be considered approximately valid.

Accepting these differential equations as approximately valid, it is possible to construct a more general mathematical theory of aqueous humor dynamics than has heretofore been available. The application of this theory makes possible the resolution of a number of apparent contradictions in the literature on aqueous humor dynamics.

Washington University Medical School (Dr. Becker).

## REFERENCES

1. Kinsey, V. E.: Dehydroascorbic Acid and Ascorbic Acid in the Aqueous Humor of Rabbits, Am. J. Ophth. **33**:257, 1950.

2. Kinsey, V. E.: The Chemical Composition and the Osmotic Pressure of the Aqueous Humor and Plasma of the Rabbit, J. Gen. Physiol. **34**:389, 1951.

3. Kinsey, V. E.: Comparative Chemistry of Aqueous Humor in Posterior and Anterior Chambers of the Rabbit Eye: Its Physiologic Significance, A. M. A. Arch. Ophth. **50**:401, 1953.

4. Kinsey, V. E., and Palm, E.: Posterior and Anterior Chamber Aqueous Humor Formation, A. M. A. Arch. Ophth. **53**:330, 1955.

5. Kinsey, V. E., and Grant, W. M.: Mechanism of Aqueous Humor Formation Inferred from Chemical Studies on Blood—Aqueous Humor Dynamics, J. Gen. Physiol. **26**:131, 1942.

6. Kinsey, V. E., and Grant, W. M.: Secretion Diffusion Theory of Intraocular Fluid Dynamics, Brit. J. Ophth. **28**:355, 1944.

7. Copeland, R. L., and Kinsey, V. E.: Determination of Volume of the Posterior Chamber of the Rabbit's Eye, Arch. Ophth. **44**:515, 1950.

8. Maurice, D. M.: The Permeability to Sodium Ions of the Living Rabbit's Cornea, J. Physiol. **112**:367, 1951.

9. Kinsey, V. E.; Grant, W. M., and Cogan, D. C.: Water Movement and the Eye, Arch. Ophth. **27**:242, 1942.

10. Davson, H., and Matchett, P. A.: Kinetics of Penetration of the Blood-Aqueous Barrier, J. Physiol. **122**:11, 1953.

11. Davson, H.: Some Problems Concerning the Formation and Circulation of the Aqueous Humor, Brit. M. Bull. **9**:5, 1953.

# Lens Extraction in the Treatment of Glaucoma

EDWARD TAMLER, M.D.
and
A. EDWARD MAUMENEE, M.D., San Francisco

The purpose of this paper is to review briefly the indications for lens extraction in glaucoma and to suggest another possible indication. It has been suggested that lens extraction is indicated in the following types of glaucoma:

1. Glaucoma due to swelling or intumescence of the lens
2. Glaucoma secondary to lens-induced uveitis
3. Glaucoma due to subluxation or dislocation of the lens
4. Glaucoma associated with exfoliation of the lens capsule
5. Malignant glaucoma

In a review of cases of lens extraction for glaucoma on the Stanford University Hospital Eye Clinic service and in the private practice of one of us (A. E. M.), another indication is suggested. This indication includes cases of chronic iris-block glaucoma in an acute attack lasting 36 hours or more, with a very shallow anterior chamber and failure to respond to intensive miotic therapy. This indication will be discussed in more detail after a brief review of the indications listed above.

## GLAUCOMA DUE TO SWELLING OR INTUMESCENCE OF LENS

Glaucoma due to lens swelling occurs in eyes predisposed to acute attack by virtue of a narrow angle. Sternberg and Meyer [1] found by gonioscopic examination that the angle of the eye opposite the one with lenticular swelling was of the narrow type.

Earlier writers recommended iridectomy, followed subsequently by cataract extraction as the treatment of choice.* If the attack was of long duration and peripheral anterior synechiae were suspected, then iridencleisis was the first operation of choice, again followed at a later date by lens extraction. Guyton [4] favored combined cataract extraction in acute congestive glaucoma where the lens appeared greatly swollen.

We agree with what appears to be the prevailing opinion today, namely, that cataract extraction as the initial procedure is the treatment of choice in glaucoma due to intumescence of the lens.[5] Since this operation is usually curative, there is no apparent reason why two separate procedures need be done. If peripheral anterior synechiae are suspected, an "internal cyclodialysis" can be done at the same time as the lens extraction. One can also utilize injection (and release) of air at the same sitting in an attempt to break the synechiae.

## GLAUCOMA SECONDARY TO LENS-INDUCED UVEITIS

It is well known that free adult lens material released into the anterior chamber may give rise to iridocyclitis. This is seen clinically quite frequently in patients with retained lens cortex following rupture of the capsule during cataract extraction † and following traumatic or spontaneous rupture of the capsule of a cataractous lens.‡ It also occurs in patients with hypermature cataracts.§ In the last group it is thought

Submitted for publication Aug. 22, 1955.

From the Division of Ophthalmology, Department of Surgery, Stanford University School of Medicine.

* References 1 to 3.
† References 6 and 7.
‡ References 8 and 9.
§ References 9 to 14.

that lens material may filter through the intact lens capsule,‖ as suggested by cases of spontaneous resorption of a cataract, or it may enter the aqueous through microscopic dehiscences of the capsule.[12] Capsular dehiscences with senile cataracts may be posteriorly situated[14] and not clinically visible.

The mechanism whereby lens material, once released into the anterior chamber, sets up an iridocyclitis is not, as yet, clearly defined. It has been postulated that it may be due to an inherent or acquired hypersensitivity of the patient to lens protein.¶ Clinically, one is sometimes struck by the severe reaction following extracapsular cataract extraction in the second eye of a patient who had previously had an extracapsular extraction in the first eye. It has been recommended that patients who are shown to be sensitive to lens protein by skin test be desensitized either pre- or postoperatively.# Animals can be made into hyperreactors to their own lens material by systemic injection of lens material with adjuvant,[17] or even by other, nonspecific, systemic injections.[18] Though a histological picture has been described for such a hypersensitivity reaction,[13] no sharp line can be drawn between the histology of the hypergic reaction and the nonhyperergic reaction to lens protein.[19] More histological studies are needed in this respect.

Others have theorized that the iridocyclitis is a toxic reaction to autolyzed or decayed lens substance,* especially in cases of hypermature cataract. This might explain why a child's lens cortex material mixed with aqueous is better tolerated than an adult's.

Within this group of cases of glaucoma due to lens-induced uveitis, it is the condition of a hypermature lens with iridocyclitis that is most likely to be associated with secondary glaucoma. With increasing longevity, this entity becomes commoner, and, in recent years, more and more cases have been recognized and reported.† It occurs chiefly in two groups of elderly patients.[21] In the one group the patient has a clear lens and good vision in the other eye and therefore postpones extraction of the hypermature cataract. In the other group the patient has had a successful cataract extraction in the other eye and never gets around to having the hypermature lens removed. It has been shown that macrophages fill the angle and obstruct the trabecular meshwork in these cases.‡ It is believed that this blockage causes the glaucoma. Another theory to account for the glaucoma stipulates that mechanical trauma to the ciliary body and iris root by movement of the loose nucleus within the capsule produces a reflex vascular disturbance throughout the eye.[6] Accepted treatment consists of extraction of the hypermature cataract. It is worth repeating that these patients may show poor light projection, probably because of the edematous cornea, hazy aqueous, and milky lens acting, as Verhoeff explains, as a diffusing screen. This was one reason why, in the past, the diagnosis of absolute glaucoma was made and many of these eyes removed as blind, painful eyes.

Glaucoma has been reported to occur secondarily, too, in cases of traumatic and spontaneous rupture of the lens capsule.§ Many of the cases of spontaneous rupture had hypermature cataracts and therefore fell into the category described in the last paragraph. In the others the mechanism for production of the glaucoma is not definitely known. One theory accounts for the glaucoma on the basis of an increase in osmotic and oncotic pressure in the anterior chamber.[22] Another theory postulates overproduction of aqueous as a result of chemical irritation of the ciliary processes by lens substance.[14] Still another theory has the swollen lens material blocking the angle

‖ References 7 and 10.

¶ References 6, 13, 15, Cooper and others,[16] cited by Law.[7]

# References 6, 15, Cooper and others,[16] cited by Law.[7]

* References 7, 8, 10, and 13.

† References 8 to 14; 20.

‡ References 10, 13, and 21.

§ References 8, 9, 14, 20, and 22.

mechanically.‖ Treatment consists of removal of the lens material, supplemented by the administration of corticosteroids.¶

The term "phacogenetic uveitis" is often used to describe the reaction of the eye to lens material. Verhoeff # points out the etymological incongruity of employing this term, since it literally means that the inflammation gives rise to the lens. "Lens-induced" is a better prefix to employ. Another more suitable term, "phacolytic" uveitis, has been suggested.[21]

### GLAUCOMA DUE TO SUBLUXATION OR COMPLETE DISLOCATION OF THE LENS

Many mechanisms have been suggested for the occurrence of glaucoma secondary to partial or complete dislocation of the lens. Heath [23] mentions a number of possibilities: The lens coming in contact with the ciliary processes mechanically produces an irritative vasomotor reaction there, with edema and perhaps increased permeability, and increased aqueous formation. If the lens is pushed forward, the angle of the anterior chamber may be partly blocked by the root of the iris against the cornea. If the lens is luxated into the anterior chamber, it may block the pupillary space. Finally, the dislocated lens may set off a uveitis, which then leads to secondary glaucoma. Chandler and Johnson [25] mention the possibility of a pupillary block by vitreous pushed into the pupillary space by the posterior dislocation of the lens. Barkan [26] describes a case of anterior displacement of the lens, producing increased physical contact between the iris and the lens. This resulted in an increased functional seclusion of the pupil. With obstruction of passage of fluid through the pupil there followed an iris bombé with blockage of the filtration angle by the root of the iris.

Where the glaucoma is due to a pupillary block, as cited in the last two references, the establishment of a communication between the anterior and the posterior chamber would be curative. However, generally in cases of glaucoma secondary to lens dislocation, lens extraction is the accepted procedure of choice.*

### GLAUCOMA ASSOCIATED WITH EXFOLIATION OF THE LENS CAPSULE

There still exists considerable controversy regarding the causal relationship of exfoliation of the lens capsule and glaucoma. Since Vogt's classical papers,† describing in clear detail the picture of capsular exfoliation and suggesting it as a direct cause of glaucoma, there have been many reports of cases manifesting both conditions. A causal relationship was strongly suggested by the high incidence of glaucoma reported in patients with exfoliation. Tabulation of the reports on combined incidence and a summary of the literature up to 1940 are contained in reviews by Irvine,[31] Gradle and Sugar,[32] and Duke-Elder.[33] The percentage of patients with exfoliation who have glaucoma ranges from 4% to 90%, with an average of about 50%. Most of these statistics come from eye clinic populations with symptoms and are therefore somewhat weighted toward the higher percentages. Symptomless cases of exfoliation would probably show a lower percentage of concomitant glaucoma. Although often occurring unilaterally,[32] exfoliation is considered to be a senile condition and rarely occurs below the age of 50. The incidence of exfoliation in persons over 50 years of age has been variously reported to be from 2% to 18%. Such figures depend heavily on the degree of thoroughness of the examination.[31] There is also a wide variation in the figures reported for the incidence of exfoliation in patients with chronic simple glaucoma, the figures ranging from 6% to 93%. Again, thoroughness of examination is an important factor.

‖ References 20 and 23.

¶ References 8, 9, 14, 20, and 24.

# Verhoeff, F. H., in discussion on Irvine and Irvine.[18]

* References 23, 27, and 28.

† References 29 and 30.

More recent statistics on the same subjects ‡ also fall within the limits mentioned above.

The relatively high average incidence of glaucoma in patients with exfoliation has led many clinicians to conclude that there must be a causal relationship between the two. Irvine [31] believes the relation between the two conditions to be significant but does not go so far as to say that the glaucoma is directly caused by the exfoliation. Gradle § thought that capsular exfoliations are the cause of glaucoma in a certain percentage of cases, depending entirely on the size of the exfoliated material and on how much of the iridocorneal angle was thereby blocked. Both Barkan [37] and Gradle and Sugar [32] report the finding of exfoliated material in the filtration angle. Gradle and Sugar believe that the capsular exfoliations are carried by aqueous flow to the chamber angle, where they cover the trabeculae. When more than 65 degrees of the angle circumference is covered, a pathological rise in intraocular pressure results. Terry ‖ thought that in an eye in which glaucoma was prone to develop, only a small amount of foreign material in the iridocorneal angle could be the final exciting factor. Heath [23] states that the percentage of glaucoma occurring in patients with capsular desquamation is high enough to be significant. He believes that desquamation may produce glaucoma by toxic, irritative, and mechanical methods but that increased hyalinization and sclerosis of the trabeculae may be associated with flaking of the capsule. He mentions that patients with glaucoma in both eyes and desquamation in one eye show consistently higher tension levels on the exfoliating side. On the other hand, Trantas [38] reports a case in which there was glaucoma and no exfoliation in one eye and exfoliation without glaucoma in the other eye. Duke-Elder [33] feels it is probable that a clogging of the filtration angle with capsular debris acts as a predisposing cause in determining the development of glaucoma, which might remain clinically latent were the efficiency of the drainage angle unimpaired. Theobald [39] describes three cases with a clinical diagnosis of glaucoma associated with an exfoliating lens capsule. Histologically, there was no true exfoliation of the lens capsule, but, rather, precipitates or accretions of an unknown substance on anterior segment structures. She calls this condition "pseudoexfoliation of the lens capsule" and believes that most cases of senile exfoliation fall into this category. Microscopically, debris filled the intratrabecular spaces and even the canal of Schlemm. Presumably, this blocked escape of aqueous, thereby producing a condition directly favoring an increase in intraocular pressure.

Kirby ¶ believed that the incidence of glaucoma in cases of exfoliation did not prove that the latter caused the former but merely showed that the two were coincidentally associated in a larger degenerative process. Bedell # found one case only of glaucoma in 26 consecutive cases of capsular exfoliation, but the period of observation is not given. Ross [34] reports a case of acute congestive glaucoma with exfoliation of lens capsule in a patient with a narrow angle. He concludes that the congestive glaucoma was probably independent of the exfoliation. Weekers and associates * studied 14 cases of capsular glaucoma and pointed out the similarity in clinical features and course to chronic simple glaucoma. They found the angle changes inconstant and the appearance of aqueous veins normal. They believe the elevated tension is not due to obstruction of the angle, since the elevation may precede obstruction. Wilson [36] concludes that capsular exfoliation is not the essential cause of glaucoma capsulare because it is often present without increased intraocular pressure and because the clinical

‡ References 34 to 36.

§ Gradle, H. S., in discussion on Irvine.[31]

‖ Terry, T. L., in discussion on Irvine.[31]

¶ Kirby, D. B., in discussion on Irvine.[31]

# Bedell, A. J., in discussion on Irvine.[31]

* References 40 and 41.

association of the two conditions is so inconsistent.

It is apparent that the statistics on the combined incidence of exfoliation and glaucoma can be used to bolster or attack the theory of a causal relationship. From the information available at the present time, it seems we may only conclude that, although both conditions are probably a part of a generalized senile ocular degenerative process, the continued deposition of capsular debris in the angle and in the trabecular spaces may contribute to the elevation of tension in an eye disposed to open-angle glaucoma.

It follows, then, that lens extraction is not indicated in glaucoma capsulare unless the lens is cataractous. Irvine [31] feels that the possibility of weak zonules, fluid vitreous, and friable capsule in these cases makes for poorer operative prognosis with lens extraction. Kirby † denies the presence of excess fragility of the capsule. He feels that the only logical treatment is a filtering operation. Gradle and Sugar [32] suggest miotics as the first mode of therapy. Where a cataract is present, lens extraction may be done if the tension is first controlled. An uncontrolled case requires antiglaucomatous surgery first, whether the lens is clear or cataractous. Extracapsular extraction is suggested because of the frequent finding of fluid vitreous. Weekers and associates * recommend cyclodiathermy if the tension is not above 40 mm. Otherwise, iridencleisis is suggested. Wilson [36] prefers miotics or a decompression operation.

### MALIGNANT GLAUCOMA

Malignant glaucoma refers to those cases of glaucoma in which surgical intervention is promptly followed by a flat anterior chamber and an elevated tension, both of which are unresponsive to further measures. It is more commonly seen with chronic iris-block glaucoma than with other types of glaucoma. In his discussion of factors predisposing to malignant glaucoma, Chandler [42] states that in all reports of this condition, where a detailed preoperative examination of the eye is recorded, the anterior chamber was very shallow and the preoperative tension high. He believes it is commoner in chronic than in acute congestive glaucoma. He notes that von Graefe stated that it occurred only in chronic glaucoma. He mentions the fact that it has been reported in acute glaucoma, but the cases for the most part were neglected ones in which the attack was of two days' to several weeks' duration before treatment was undertaken.

The treatment of malignant glaucoma usually resolves itself into a series of unsuccessful surgical procedures, ending with the loss of the eye. The mechanism of this train of events is unknown. Shaffer [43] suggests pupillary block with vitreous detachment as a possible mechanism. According to this theory, the aqueous runs posteriorly because of the pupillary block. It may collect behind a detached vitreous, which forces it and the iris forward, making it impossible to refill the anterior chamber. Barkan [44] states that a leaky wound may initiate a malignant course in a predisposed eye, since it encourages a forward displacement of the lens-iris diaphragm. He also suggests for consideration a possible relationship between malignant glaucoma and the fact that the zonular anterior hyaloid diaphragm is relatively impermeable to passage of fluid from behind forward.

Although reports are few, it is generally believed that malignant glaucoma in one eye presages the development of malignant glaucoma in the other eye if the latter is subjected to intraocular surgery.[42]

It is generally agreed that lens extraction is the operation of choice for malignant glaucoma.‡ Barkan [44] would do an intracapsular lens extraction if an iridectomy and vitreous aspiration were not immediately effective in cases in which the first eye developed a malignant course, although he notes that further experience may indicate that initial lens extraction is preferable.

† Kirby, D. B., in discussion on Irvine.[31]

‡ References 42 and 45.

To be successful in most cases, the extraction must be done as a primary procedure. For some unknown reason, when done as a secondary or tertiary procedure, it is technically more difficult, fraught with complications, and usually unsuccessful in halting the inexorable downhill course initiated with the first procedure. According to Shaffer's theory of malignant glaucoma, surgical treatment should be directed toward breaking the pupillary block either by iridectomy or by an actual incision through the detached vitreous.[43] Wegner [46] recommends a double iridectomy through ab externo incisions for malignant glaucoma. The incisions are made 1 to 1.5 mm. behind the limbus at 10 and 2 o'clock, leaving about a 3 mm. bridge of sclera between. The two iridectomies are joined by delivering the first iris pillar through the second incision, giving one continuous wide iridectomy. Wegner states that this operation, done as a secondary procedure, saved the eye in eight typical cases of malignant glaucoma. In four of these cases pilocarpine was required postoperatively. In the other four the tension was normal without medication. In two cases in which the first eye was lost due to malignant glaucoma, Wegner was able to maintain satisfactory function of the second eye with the operation. None of the 10 cases is described.

The difficulty in the treatment of malignant glaucoma resides in the fact that, except for patients with a history of the disease in the other eye, one cannot tell in advance of surgery which of his cases will take this malignant course. A shallow anterior chamber preoperatively and an elevated tension at the time of operation are prerequisites for such a development; but of the cases meeting these requirements, only a very small percentage will go on to develop malignant glaucoma. Thus, because of the inability to predict malignant glaucoma in advance of surgery and the statistical odds against its occurrence, ophthalmic surgeons are reluctant to remove a clear lens for an acute rise in tension during the course of a chronic iris-block glaucoma.

### POSSIBLE ADDITIONAL INDICATION

Another indication for lens extraction suggested itself to us in retrospect while we were going over records of cases of chronic iris-block glaucoma. This consists of advanced iris-block glaucoma in an acute attack with the following characteristics:

1. History of previous attacks of iris-block glaucoma

2. A history of elevated base pressure

3. A very shallow anterior chamber at the time of the latest attack

4. A high tension, over 40 mm. Schiøtz, with the acute attack, which has been in existence for 36 hours or more and has failed to respond to intensive miotic therapy

It has been difficult to find reports of the surgical treatment in such a group of cases. About the closest we can get to the above-outlined category are a few reports in which some of the cases of iris-block glaucoma are spoken of as chronic congestive, late, advanced, or long standing, these terms being based primarily on field loss, loss of visual acuity, recurrent rise in tension, and the formation of peripheral anterior synechiae.

It is generally felt that iridectomy alone is not the operation of choice in chronic iris-block glaucoma.§ In a series of 18 iridectomies for acute congestive glaucoma, Kronfeld and McGarry [47] reported success in only 38%, and these were predominantly in early cases. They note that the great majority of unsuccessful iridectomies occurred in eyes with advanced congestive glaucoma, and they conclude that iridectomy is suited only for the early stages of the disease. Sourdille [48] reaches the same conclusion. Haas and Scheie [50] state that iridectomy should be employed only during the first 36 hours of the first attack, or during the interval phase between attacks if the tension remains normal with or without miotics. In discussing the same paper, and in his own writings,[49] Chandler states that peripheral iridectomy or iridotomy will be

§ References 44 and 47 to 52.

ineffective if the glaucoma is advanced and a large part of the angle is permanently closed by peripheral anterior synechiae. In analyzing the relation of angle occlusion, outflow, and congestion in chronic congestive glaucoma, Goldmann [51] concludes that iridectomy is not successful by itself. Barkan [44] believes that iridectomy is relatively ineffective in late cases of narrow-angle glaucoma because, in addition to angle adhesions, there may be damage to the trabeculum by transient contacts between it and the iris root.

With regard to iridencleisis, Reese [63] states that it is not indicated in advanced glaucoma with peripheral anterior synechiae. Chandler [49] recommends this operation in chronic narrow-angle glaucoma with synechiae.

In a recent article involving a relatively large series of cases of acute congestive glaucoma treated at the Wilmer Ophthalmological Institute between 1930 and 1946, Goldberg [54] summarizes the operative results obtained with various procedures in different stages of the disease. He divided the cases into three groups: The first group contained those cases in which the disease was very advanced, with very little vision remaining, and which possessed extensive organic changes from prior recurrent attacks. His second group consisted of recurrent cases in which, generally, the disease had been uncontrolled by miotics or previous surgery but in which the organic changes were not advanced. These two groups, except as noted below, include the cases that are roughly comparable to the type of cases we are concerned with here. We are not concerned with his third group of patients, usually in their first attack, with few, if any, organic changes.

The first group was treated with posterior sclerectomy or sclerotomy combined with an anterior segment operation—iridectomy, iridencleisis, or corneoscleral trephine. Complications and failures were the rule, and in only 13% was the surgery successful.

The second group was treated with iridencleisis. Success in 78% is reported. However, in almost two-thirds of the successful group the operation was performed after the tension fell to normal in response to miotics. If we discard from consideration those cases responding to miotics preoperatively, we are left with 23 cases which responded poorly to miotics preoperatively, of which 16, or 69%, were successfully treated by iridencleisis.

Now, if a patient with recurrent acute glaucoma were to present himself in an acute attack, it would frequently be impossible to classify him in one of Goldberg's first two groups. Therefore, combining the results in the above two groups, there was a total of 55 cases, of which 19, or only 35%, had successful surgery.

Of 10 eyes with chronic congestive glaucoma and cataract, Guyton [4] treated 6 with a fistulizing operation first and cataract extraction later. Of these, two were controlled by the fistulizing operation, and the other four were finally controlled by additional glaucoma operations. None of these four were controlled by cataract extraction. The other four cases of chronic congestive glaucoma and cataract were treated initially with cataract extraction (two intracapsular and two extracapsular). In three the tension was normal without miotics postoperatively. In one case the tension rose in two weeks after operation but no further surgery was performed. Guyton concludes that in eyes with chronic congestive glaucoma a combined cataract extraction as the initial procedure offers at least as much chance as, and probably more than, a fistulizing operation performed first.

In recent years, on the Stanford University Hospital clinic service and in the private practice of one of us (A. E. M.), a total of 10 patients, involving 15 eyes, with acute iris-block glaucoma were treated with lens extraction. These cases are, for the most part, similar in type and stage to those discussed above. The case histories are summarized later in this paper and the results tabulated (Table).

In 14 of the 15 eyes there was a history of a previous period of elevated tension. In

| Case No. | Sex | Age | Eye | Glaucoma History | Preoperative: Tension, Mm. | Preoperative: Chamber | Operation | Result |
|---|---|---|---|---|---|---|---|---|
| 1 | M | 62 | R. E. | Bilat. congen. microphthalmos, high hyperopia, and narrow-angle glaucoma<br>Acute cong. attack L. E., unsuccessfully treated by iridectomy, then lens extraction<br>R. E.: Base pressure elevated in spite of miotics and vision decreasing | 40-50 | Extremely shallow, almost obliterated in periphery | Intracap. lens extrac. (mod. post. cortical opacity) | Tension normal without miotics; chamber normal depth; follow-up 3½ yr. |
| 2 | M | 84 | L. E. | Glaucoma R. E. unsuccessfully treated by trephination, later enucleated<br>Chronic iris-block glaucoma L. E. uncontrolled by miotics recently, with decreasing vision | 40 | Extremely shallow, partially obliterated peripherally | Intracap. lens extrac. (mod. nuclear and cortical opacities) | Tension normal without miotics; chamber normal depth<br>Gonioscopy: Many P. A. S. with occasional opening in angle; follow-up 5½ yr. |
| 3 | M | 71 | R. E. | In acute attack; no prior history of glaucoma but cupping of disc and baring of blind spot on exam. | 72+ | Very shallow | Intracap. lens extrac. (slight cortical opacities) | Tension normal; chamber normal depth; 5-mo. follow-up |
| | | | L. E. | Several acute attacks in past; tension uncontrolled by miotics; pain and decreased vision | 48-72+ | Almost flat | Intra-extracap. lens extrac. (mod. nuclear and cortical opacities) | A. C. normal depth but superior half of angle obstructed; persistent iritis, leading to 2° glaucoma; 4-mo. follow-up |
| 4 | M | 58 | R. E. | 2° glaucoma L. E., unsuccessfully treated by miotics, surgery, and x-ray<br>Glaucoma R. E. uncontrolled by miotics, cyclodialysis, iridencleisis, another cyclodialysis, posterior sclerotomy, and air injection to deepen A. C.<br>In acute cong. attack | 49-69 | Deep centrally but extremely shallow peripherally | Paracentesis and int. cyclodialysis, followed in 4 days by intracap. lens extrac. (mod. opacities) | Tension normal with miotics; chamber normal depth<br>Gonioscopy: Many P. A. S. with occasional opening, exposing trabeculum; 4½ yr. follow-up |
| 5 | M | 71 | L. E. | Glaucoma O. U., controlled in R. E. with miotics, uncontrolled L. E.<br>In acute attack L. E. | 40-67 | Shallow | Intracap. lens extrac. (immat. cat.) | Tension normal; chamber normal depth; 2-mo. follow-up |
| 6 | F | 66 | L. E. | On miotics for iris-block glaucoma; previous acute attack; now again in acute attack | 65 | Very shallow | Intracap. lens extract. (early lens opacity) | Tension normal without miotics; chamber normal depth<br>Gonioscopy: angle ⅛ open; 3½ yr. follow-up |
| | | | R. E. | On miotics for iris-block glaucoma; episodes of pain and decrease in vision; entered in acute attack | 50 | Very shallow | Intracap. lens extrac. (early lens opacity) | Tension normal without miotics; chamber normal depth<br>Gonioscopy: Angle open; 2 yr. follow-up |
| 7 | F | 76 | R. E. | Acute attack for 9 days | 48 | Shallow with narrow periphery | Intracap. cat. extrac. (dense nuclear sclerosis) | Tension normal without miotics; chamber normal depth; 2½ yr. follow-up |
| | | | L. E. | Poorly controlled narrow-angle glaucoma; entered with acute rise in tension | 63 | Same | Same | Tension normal without miotics; chamber normal depth; 1½ yr. follow-up |
| 8 | F | 59 | R. E. | Acute attacks, poorly controlled by miotics, iridectomy and 2 cyclodiath.; microphthalmos; high hyperopia, and retinitis pigmentosa | 45 | Very shallow; angle almost completely closed | Intracap. lens extrac. (slight lens opacities) | Tension normal on miotics; chamber normal depth<br>Gonioscopy: Angle generally closed by P. A. S. exc. superiorly; follow-up 1¾ yr. |
| | | | L. E. | Acute attacks poorly controlled by miotics and iridencleisis; microphthalmos, high hyperopia, and retinitis pigmentosa | 45 | Almost flat | Same | Tension normal on miotics; chamber normal depth<br>Gonioscopy: Angle generally open with occasional P. A. S.; follow-up 1½ yr. |
| 9 | M | 70 | L. E. | Acute cong. glaucoma R. E. unsuccessfully treated by iridectomy, iridencleisis, and lens extrac.; eventually R. E. enucleated<br>Transient episodes of blurred vision L. E.; entered in acute attack | Eye stony-hard | Very shallow centrally; flat peripherally | Intracap. lens extrac. (sl. post. cortical opacities) | Tension normal without miotics; chamber normal depth<br>Gonioscopy: Angle open; one P. A. S.; 2 yr. follow-up |
| 10 | F | 75 | L. E. | Acute attack temporarily controlled by retrobulbar procaine and miotics; another acute attack a few days later | 80 | Extr. shallow; iris against cornea | Intracap. cat. extrac. (fairly dense cat.) | Tension normal without miotics; ant. chamber normal depth<br>Gonioscopy: Angle closed by P. A. S. exc. superiorly; iris included in wound; 1½ yr. follow-up |
| | | | R. E. | Acute attack temporarily controlled by retrobulbar procaine and miotics; a week later another acute attack occurred | 70 | Extr. shallow | Same | A. C. normal depth; tension normal without miotics<br>Gonioscopy: Angle open inf. and temp.; iris pigment on trabeculum; iridectomy pillars adherent to wound; 1½ yr. follow-up |

one eye with no prior history of glaucoma (Case 3, R. E.) examination revealed baring of the blind spot and cupping of the optic disc. In nine eyes there was a history of an elevated base pressure. In 14 eyes the anterior chamber was very shallow to almost flat. In the one exception (Case 4), although the chamber was moderately deep centrally, it was extremely shallow peripherally, and the patient had previously undergone a posterior sclerotomy and an injection of air to deepen it. The preoperative tension was 38 mm. or higher in every case. All 15 eyes responded poorly to miotics preoperatively. The duration of the existence of the presenting elevated tension before surgery was approximately 12 to 24 hours in 1 eye (Case 6, R. E.), 24 to 36 hours in 2d eye (Case 3, R. E.), 36 to 48 hours in a 3d eye (Case 9), 48 hours in a 4th eye (Case 10, R. E.), and 3 days or more in 10 additional eyes. In one eye (Case 7, L. E.) the duration was not known. In three eyes visual fields were apparently normal (Cases 1, 6, R. E., and 9). In three eyes fields were not obtained (Case 7, L. E., and Case 10, O. U.). Nine eyes showed varying degrees of field loss, tested either pre- or postoperatively, but the preoperative fields were not considered accurate. In 10 eyes the acute attack was severe, with pain, congestion, and corneal edema. In five eyes (Cases 1, 2, 7, L. E., and 8, O. U.) the attack consisted primarily of an uncontrolled rise in pressure. In 12 eyes the lens extraction was the first surgical procedure done for the glaucoma. In three eyes (Cases 4 and 8, O. U.) the patients had had previous glaucoma surgery. In 11 eyes the extracted lens either was relatively clear or contained mild opacities. Only four eyes had moderately dense (Case 10, O. U.) or dense (Case 7, O. U.) cataracts. Five lenses were extracted by sliding technique (Cases 7, L. E.; 8, O. U., and 10, O. U.); the others, by tumbling. In 10 eyes a full iridectomy was used. Basal iridectomy was employed in two eyes (Cases 4 and 5), and a round-pupil iridotomy in one eye (Case 6, L. E.), and in two eyes there were iridectomies already present from previous surgery (Case 8, O. U.). Fourteen lenses were delivered intracapsularly. One capsule was broken (Case 3, L. E.) and had to be extracted by hand-over-hand technique. In six eyes (Cases 4, 5, 6, L. E.; 7, R. E., and 8, O. U.) an attempt was made to free peripheral anterior synechiae. Fluid vitreous was lost in one eye (Case 5), and in another eye (Case 3, L. E.) there was a postoperative adhesion of the vitreous face to the wound. One case (Case 1) is reported to have a liquid vitreous three and a half years after operation. In Case 2 there is no record of the integrity of the vitreous face. In the remaining 11 eyes the vitreous face was intact postoperatively. The follow-up period for four eyes was three years or more (Cases 1, 2, 4, and 6, L. E.). Three eyes have been followed for two to three years (Cases 6, R. E.; 7, R. E., and 9). Five eyes (Cases 7, L. E.; 8, O. U., and 10, O. U.) have been followed from one to two years. Three eyes were followed for less than six months (Cases 3, O. U., and 5).

A further, though minor, reason for performing lens extraction on these patients was the feeling that there was a greater possibility that malignant glaucoma would develop in this group of iris-block glaucoma than in other types.[45] However, the more important consideration was the usual poor result in this type of glaucoma with other surgical methods.

In all the cases reported here, the tension was normalized and the anterior chamber deepened following lens extraction. However, in one eye (Case 3, L. E.) the tension rose again after a few months, due to the establishment of a secondary glaucoma. None of the other eyes required any further glaucoma surgery. In another eye (Case 10, L. E.) a small piece of iris was inadvertently included in the wound. Since by gonioscopy the angle in this eye is closed by synechia, and cystic conjunctival blebs were noted in the region of the inclusion, there is good reason to believe that the unscheduled iris incarceration is functioning to carry off aqueous.

The decision to perform a lens extraction was made easier in five eyes (Cases 3, L. E.; 6, R. E.; 7, L. E.; 8, L. E., and 10, R. E.) by the fact that the other eye was already aphakic. There was also little difficulty in deciding to do a lens extraction in the eyes with dense cataracts and in Case 9, where there was a history strongly suggesting malignant glaucoma in the other eye. In three additional eyes (Cases 1, 2, and 4) the other eye was blind, or almost blind, so that the problem of monocular aphakia in the presence of a normal phakic other eye did not have to be considered. That the problem of monocular aphakia would be short-lived in many cases is suggested by the finding in the Wilmer Institute series [54] that acute glaucoma occurred in both eyes in 72% of cases within six months. Furthermore, glaucoma surgery often accelerates cataract formation, necessitating subsequent cataract extraction. Even if these arguments were not cogent, we are inclined to agree with the statement that monocular aphakia is a small price to pay for the curing of glaucoma.

The mechanism whereby lens extraction in these cases resulted in normalizing the ocular tension is not known. Postoperative gonioscopy was performed in nine of the eyes (Cases 2; 4; 6, O. U.; 8, O. U.; 9, and 10, O. U.). In four eyes the angle was generally closed by synechia (Cases 2; 4; 8, R. E., and 10, L. E.), and yet the tension was controlled. We have already mentioned the accidental iris inclusion in Case 10, L. E. In two eyes the angle was partially open (Case 6, L. E., and Case 10, R. E.). In three eyes the angle was generally open (Cases 6, R. E.; 8, L. E., and 9). In all cases the deepening of the anterior chamber postoperatively suggests a concomitant widening of the angle, except where permanent adhesions existed.

In the three eyes that were microphthalmic (Case 1 and Case 8, O. U.) the absolute values of the tonometric readings may have been inaccurate because of the presence of microcornea. However, other findings left little doubt of the existence of glaucoma. In addition, the tension in these eyes dropped to normal levels after surgery.

Since these cases were done, acetazoleamide (Diamox) has come upon the scene. What effect the use of this drug will have upon the operation of choice in chronic advanced congestive glaucoma cannot be determined at the present time.

## CONCLUSIONS

The indications for lens extraction in glaucoma are reviewed.

Extraction appears indicated in intumescence, phacolytic glaucoma, glaucoma secondary to a dislocated lens, and malignant glaucoma, but its value is doubtful in glaucoma capsulare.

In addition, lens extraction is suggested in advanced cases of acute iris-block glaucoma with a very shallow anterior chamber and a high tension which does not respond to medication, or in cases in which the patient has been in the acute attack for three days or more. This suggestion is made even when the lens is clear, but especially when the lens is already moderately to densely opaque or when the other eye is already aphakic.

## REPORT OF CASES

CASE 1.—A 62-year-old man was seen for the first time in November, 1947, with a history of bilateral congenital microphthalmos, high hyperopia, and narrow-angle glaucoma. The left eye had previously been treated for an attack of acute congestive glaucoma with an iridectomy, followed in one month by a lens extraction. Since that time vision in the L. E. had been limited to light perception with poor projection. The tension in the R. E. had been running slightly above normal in spite of intensive therapy with miotics, and vision in that eye had been gradually decreasing.

Examination of the R. E. disclosed a marked microphthalmos. The anterior chamber was extremely shallow, being almost obliterated in the periphery. Corrected acuity was 20/100, and there was a moderate posterior cortical lens opacity. Visual field was apparently normal, although the blind spot could not be plotted satisfactorily. Tension ran between 40 and 50 mm.

Continued miotics failed to reduce the tension in the R. E. An intracapsular cataract extraction with full iridectomy was done. The postoperative course was uneventful. The chamber deepened, and the ten-

sion dropped to normal levels. When he was last seen in 1951, the tension was recorded as 24 mm. (Schiøtz), and vision was 20/100 with a +21.00 sph ⊂ +1.00 cyl, ax 150. He was not using miotics.

Case 2.—An 84-year-old man was first seen in August, 1949, when referred for treatment of poorly controlled narrow-angle glaucoma L. E. The patient had had glaucoma in the R. E., which had failed to respond to trephination, and the eye was enucleated in 1947. At that time, glaucoma was discovered in the left eye, and he was placed on miotics. Recently his tension was not controlled by drops, and his vision began to decrease.

Examination revealed correctible acuity of 20/200 with the L. E. The pupil measured 1.5 mm. in diameter and reacted only slightly to light. The cornea was clear. The anterior chamber was extremely shallow, and the iris appeared to touch the periphery of the angle in many places. Only a red reflex was obtained by ophthalmoscopy through the small pupil and nuclear and cortical lens opacities. Tension was 40 mm. (Schiøtz). Field test showed a superior nasal field defect and an extensive Bjerrum scotoma.

Intracapsular extraction of the lens with full iridectomy was performed. The chamber deepened in a few days. Eleven days postoperatively the tension measured 18 mm. (Schiøtz). The patient has been followed for five and a half years, during which time his tension has been normal without miotics and his anterior chamber has remained at normal depth. There is some cupping and pallor of the optic disc. Visual acuity in March, 1955, was 20/25 corrected. Gonioscopy reveals extensive closure of the angle by peripheral anterior synechiae with openings at the 2, 6, 10, and 12 o'clock positions.

Case 3.—A 71-year-old man was referred in March, 1950, for emergency treatment of bilateral acute narrow-angle glaucoma. There was a history of previous attacks of glaucoma in the L. E.

Examination showed a visual acuity of 20/40 with the R. E. and hand movements at 10 ft. with the L. E. The right cornea was slightly cloudy; the left, definitely edematous. Both anterior chambers were very shallow, the left being almost flat. The right lens contained only slight diffuse cortical opacities. The left lens had moderate nuclear and cortical opacities. There was glaucomatous cupping of both discs, seen through the cloudy media. Tension was above 72 mm. (Schiøtz) in each eye. Central fields revealed baring of the blind spot in the R. E. with 2/1000 white and constriction to within 10 degrees in the L. E. with 5/1000 white. There were numerous large pigment deposits on the back of the left cornea.

Intensive miotic therapy was given for six hours, without response. It was decided to operate on the R. E. because of the poor prognosis for the L. E. An intracapsular lens extraction, R. E., was performed with full iridectomy. The chamber deepened and the tension was soft postoperatively. The chamber remained deep; tension remained normal, and visual acuity was 20/20 with aphakic correction. Visual field showed moderate constriction.

The tension in the L. E. continued to be poorly controlled by miotics, and the patient experienced episodes of pain in that eye. Therefore an intracapsular extraction was attempted in the L. E. The capsule ruptured during extraction of the lens, but all of the capsular material was removed. A full iridectomy was employed. The chamber was deep postoperatively, and the tension was within normal limits for several months. However, all during this postoperative period the L. E. manifested a moderate ciliary flush, corneal edema, striate keratopathy, slight aqueous flare, and adherence of the vitreous face to the wound. The angle appeared obstructed from 10 to 2:30 o'clock. A secondary glaucoma ensued, and the tension rose gradually to 55 mm. Response to both miotics and cycloplegics was poor. Cyclodialysis was recommended but was consistently refused. Tension remained elevated; field gradually shrank to less than 5 degrees; vision dropped to perception of hand movements at 1½ ft. and central fixation became doubtful.

Case 4.—A 58-year-old man was referred for treatment of an uncontrolled iris-block glaucoma, R. E., in August, 1950.

The patient had a history of bilateral cataract. One year before he had had a cataract extraction, L. E., followed by secondary glaucoma. He was treated with miotics, surgery, and x-ray therapy, but these measures failed, and he lost the vision in his left eye. More recently glaucoma was discovered in his R. E. This was treated in succession by miotics, cyclodialysis, iridencleisis, and, finally, another cyclodialysis, all of which failed to control the tension. On one of these occasions a posterior sclerotomy and air injection was done to deepen the anterior chamber.

Examination revealed that the R. E. was intensely injected and there was a small hyphema in the anterior chamber. Only a red reflex was obtained with the ophthalmoscope. There was some edema of the corneal epithelium. The anterior chamber was moderately deep centrally but became extremely shallow in the periphery. Visual acuity was counting fingers at 3 ft. The peripheral field was grossly normal. There was a moderate lens opacity. Tension was 49 mm. (Schiøtz).

The patient was placed on miotics. The tension remained elevated. A paracentesis and internal cyclodialysis were performed, without effect. Dibenamine caused a transient drop in intraocular pressure. An intracapsular lens extraction was performed. The tension wavered for a few weeks. One

month postoperatively the tension was normal with drops and the anterior chamber was deep. Visual acuity was 20/25 with correction, and the visual field measured approximately 25 degrees with 10/1000 white. Four and one-half years postoperatively tension was still controlled with drops and acuity was 20/50. Gonioscopy showed many peripheral anterior synechiae occluding the angle, with occasional openings exposing the trabeculum.

CASE 5.—A 71-year-old man was seen in December, 1950, complaining of pain in the L. E. of three days' duration. He had a history of bilateral glaucoma, controlled with miotics in the right eye, but uncontrolled in the left. Recently he had an acute attack in the L. E., with loss of vision and pain, treated at another hospital with miotics.

Examination revealed a visual acuity of 20/25 in the R. E. and perception of hand movements at 1 ft. with the L. E. The conjunctiva of the left eye was injected and the cornea edematous. The right eye had slight bedewing of the cornea. Both pupils were irregular and in middilatation. Tensions were 40 mm. R. E. and 67 mm. L. E. (Schiøtz). Both anterior chambers were shallow and there were bilateral immature senile cataracts. Neither eye showed an aqueous flare or cells. The visual field was constricted in both eyes, more so in the left.

Intensive miotic therapy promptly brought the pressure in the right eye down to normal but had little effect on the tension in the left eye. Air was injected into the left anterior chamber in order to separate any peripheral anterior synechiae that might have been present. This failed to benefit the patient, and so an intracapsular lens extraction was performed on the left eye.

The chamber deepened postoperatively, and tension fell to normal. The patient returned to his local eye clinic in February, 1951.

CASE 6.—A 66-year-old woman was first seen in May, 1951, complaining of severe pain in the L. E. of one day's duration.

The patient had been under the care of another eye doctor for iris-block glaucoma and was using miotics in both eyes. She had had a previous episode of pain in the L. E. one week before, with blurring of vision.

Examination revealed acuity of 20/40 R. E. and 2/200 L. E. Slit-lamp examination of the R. E. showed a shallow chamber. In the L. E. the cornea was edematous, the chamber very shallow, the pupil irregular, and the lens mildly cataractous. The visual field of the R. E. was normal; that of the L. E. showed a superior temporal constriction. A red reflex was seen by ophthalmoscopy in the L. E. The right fundus was not remarkable except for questionable cupping of the disc. Tensions were 12 mm. R. E., and 65 mm. L. E. (Schiøtz). Gonioscopy performed on the right eye revealed that only the first part of the trabeculum was visible, and in some places even this was covered.

An intracapsular lens extraction, L. E., with peripheral iridotomy and freeing of anterior and posterior synechiae, was performed. The tension fell to normal, and the chamber deepened. Some posterior synechiae persisted.

In June, 1952, she began to have transient episodes of pain and decreased vision in the R. E. One month later she entered the hospital in an acute attack, R. E., with a tension of 59 mm. (Schiøtz). An intracapsular lens extraction with full iridectomy was performed after the patient failed to respond to intensive miotic therapy. The tension was within normal range postoperatively, and the anterior chamber became deeper.

The tension in both eyes has remained normal without miotics up to the time of the last visit, in October, 1954. Vision is 20/25 in each eye with aphakic correction. With gonioscopy the angle in the R. E. is seen to be open and deep all around except at the pillars of the iridectomy. In the L. E. the angle is closed over two-thirds of its circumference, with a good opening over the remaining one-third. There is still some superior field loss in the L. E. and a normal field in the R. E.

CASE 7.—A 76-year-old woman presented herself in February, 1952, complaining of pain in the R. E. of nine days' duration. In addition, she had noted rapid diminution in vision of the R. E. recently. The vision in the L. E. had been poor for a number of years.

Examination revealed visual acuity of finger counting at 3 ft. in each eye. In the R. E. there were circumcorneal injection, haziness of the cornea, and a dilated, fixed pupil. Slit-lamp examination showed corneal edema in the R. E., guttate endothelial changes of both corneas, shallow chamber with narrow periphery in both eyes, and dense nuclear sclerosis of the lens in both eyes. Nothing more than a red reflex through the lens opacity could be seen in either eye with ophthalmoscopy. Tensions were 48 mm. R. E. and 29 mm. L. E. (Schiøtz). Visual field test of the R. E. showed a superior field defect.

The tension in the R. E. did not respond to miotics and retrobulbar procaine. An intracapsular cataract extraction, with scleral-placed incision and full iridectomy, was performed on the R. E. The chamber deepened, and tension returned to normal. Visual acuity did not improve significantly, primarily because of the development of endothelial-epithelial dystrophy with bullous keratitis.

The tension in the L. E., in the meantime, hovered around the high normal range in spite of miotics. Moderate corneal edema developed. Nine months after surgery on the R. E., the L. E. suddenly be-

came involved in an acute episode of iris-block glaucoma, the tension rising to 63 mm. (Schiøtz).

An intracapsular cataract extraction L. E. was performed, using a scleral-placed incision, full iridectomy, and sliding technique. Postoperatively the chamber gradually deepened and the tension dropped to normal. As in the other eye, the corneal dystrophy progressed to a bullous keratitis.

Both eyes have maintained normal tension without miotics up to time of last visit, in July, 1954. The chambers are deep, but the angles cannot be seen because of the corneal edema.

Case 8.—A 59-year-old woman was referred in June, 1953, with a history of poor vision all of her life, bilateral high hyperopia, retinitis pigmentosa, and iris-block glaucoma. For the glaucoma she had undergone an iridectomy and two cyclodiathermy procedures since 1950 in the R. E., with poor control of tension. The L. E. had undergone an iridencleisis in April, 1952, which failed to normalize the tension. Miotics, including isofluorophate (D. F. P.), also failed to hold the tension below 30 mm. Schiøtz.

Examination revealed her acuity was 20/400 in the R. E. and 20/200 in the L. E., with a + 13.00 sphere for each eye. Visual fields showed marked irregular constriction bilaterally. Both globes were microphthalmic. The anterior chamber was very shallow in the R. E. and almost nonexistent in the L. E. The fundi showed peripheral pigmentary formations and some atrophy and cupping of the right disc. With gonioscopy the right iris appeared to be lying against the trabeculum in practically all positions around the circumference of the angle. The angle in the L. E. was too shallow to be examined gonioscopically. The lenses showed only slight clouding. Tension was 45 mm. (Schiøtz) in the R. E. and 35 mm. in the L. E.

The right lens was extracted intracapsularly by sliding technique, and at the same time an attempt was made to break the peripheral anterior synechiae with an internal cyclodialysis maneuver.

The tension in the L. E. in the meantime rose slightly, and a couple of months later the left lens was extracted in similar manner.

Postoperatively both anterior chambers deepened promptly, although some anterior synechiae persisted in both eyes. Tensions fell to normal levels and have remained so with the help of miotics. At the time of the last visit, in March, 1955, acuity was 20/200 in each eye and tension was 24 mm. (Schiøtz) in each eye. Gonioscopy revealed the right angle to be generally closed by synechiae, except superiorly in the region of the iris pillars and iridectomy. In the L. E. the angle was open in most areas, with an occasional adhesion between the iris and the trabeculum or cornea.

Case 9.—A 70-year-old man was referred in May, 1953, for treatment of an acute attack of iris-block glaucoma in his left eye.

The patient had a history of acute congestive glaucoma in the R. E., which did not respond to iridectomy, iridencleisis, or, finally, cataract extraction. Following this series of operations, the patient's tension remained elevated and his vision was reduced to light perception. Recently the eye had become painful and blind, and it was eventually enucleated.

The left eye had been well until recently, when the patient had several transient episodes of blurred vision. There was no loss of visual field, however, and his acuity remained approximately 20/40, due to a posterior cortical lens opacity.

The present episode began a day before referral with blurring of vision. His local eye doctor found the L. E. to be stony-hard and placed the patient on pilocarpine and physostigmine. The tension did not fall, nor did the pupil constrict.

Examination of the L. E. revealed the following: The eye was stony-hard. The cornea was steamy. The anterior chamber was flat peripherally and approximately 1 mm. in depth centrally. The iris extended forward in bombé fashion. The pupil was approximately 4 to 5 mm. in diameter and oval. Ophthalmoscopy yielded only a blurred red reflex, due to corneal and lens opacities. Acuity was 20/200.

An attempt was made to dilate the pupil with phenylephrine (Neo-Synephrine) and homatropine. The pupil dilated somewhat, but the tension did not change. Even, with general anesthesia and massage the tension did not come down appreciably. A paracentesis was performed and part of the aqueous removed. A large iridectomy was made superiorly and the lens extracted intracapsularly.

Postoperative recovery was uneventful. The chamber deepened almost immediately. On the 16th postoperative day a tension reading was taken and found to be 22 mm. (Schiøtz).

Tension had remained normal through his last visit, in March, 1955. Vision is 20/20 with correction. Gonioscopy shows an open angle with one synechia at the 5 o'clock position.

Case 10.—A 75-year-old woman was first seen in November, 1953, because of acute pain and loss of vision in both eyes, occurring while she was in the hospital under treatment for a coronary occlusion.

Her previous history failed to disclose any symptoms suggesting previous attacks of acute glaucoma. Her vision had become poorer in recent months, and her refractive error had changed from hyperopia to relative myopia.

Examination revealed visual acuity to be down to light perception in both eyes. Each eye was stony-hard. The corneas were markedly edematous.

Intensive miotic therapy and bilateral retrobulbar procaine injection brought the tensions down to an almost normal level within a few hours. There was some clearing of both corneas, allowing for closer inspection of the anterior segments. The irides were in middilatation and were virtually fixed. The anterior chambers were extremely shallow. In the left eye the iris was practically against the cornea. Both lenses showed some enlargement, and there were fairly dense bilateral cataract. The conjunctiva in both eyes was edematous. Ophthalmoscopy was completely unsatisfactory.

A few days later the pressure in the L. E. rose to 60 mm. in spite of miotics. The patient was taken to the operating room and an intracapsular cataract extraction was performed on the left eye, employing slow decompression of the chambers, full iridectomy, and sliding technique of lens removal.

Several days later the pressure in the R. E. rose to 70 mm., and therefore a similar surgical procedure was performed on that eye.

Postoperatively the tension in both eyes fell to normal levels and remained there without miotics. Grossly, the chambers appeared deeper. With gonioscopy, the angle over the inferior and temporal trabeculum of the R. E. was open. Considerable iris pigment was adherent to the trabeculum. Superiorly, in the region of the iridectomy, normal trabeculum was visible. The iris pillars were adherent to the posterior surface of the wound. In the L. E. gonioscopy revealed the angle to be completely obliterated by anterior synechiae except superiorly, where there was an area of free trabeculum. The nasal iris pillar appeared to be included in the posterior lip of the wound.

When the patient was last seen, in May, 1955, acuity was 20/25 in each eye with correction. Tension was normal in each eye. The fundi were essentially normal.

Dr. Rolf Eissler aided in translation of the references.

## REFERENCES

1. Sternberg, P., and Meyer, S. J.: Choice of Operation in Acute Glaucoma Secondary to Swelling of the Lens, Am. J. Ophth. **33**:763, 1950.

2. Spaeth, E. B.: The Principles and Practice of Ophthalmic Surgery, Ed. 3, Philadelphia, Lea & Febiger, 1944, p. 593.

3. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. III, St. Louis, C. V. Mosby Company, 1940, p. 3309.

4. Guyton, J. S.: Choice of Operation for Primary Glaucoma Combined with Cataract, Arch. Ophth. **33**:265, 1945.

5. Rychener, R. O.: Secondary Glaucoma Due to Cataract, Symposium on Secondary Glaucoma, Am. J. Ophth. **33**:1666, 1950.

6. Hughes, W. F., Jr., and Owens, W. C.: Postoperative Complications of Cataract Extraction, Arch. Ophth. **38**:577, 1947.

7. Law, F. W.: Ocular Reaction to Lens Protein, Brit. J. Ophth. **37**:157, 1953.

8. Scott, J. G.: Spontaneous Rupture of the Lens Capsule, Brit. J. Ophth. **37**:58, 1953.

9. Hubbersty, F. S., and Gourlay, J. S.: Secondary Glaucoma Due to Rupture of the Lens Capsule, Brit. J. Ophth. **37**:432, 1953.

10. Zeeman, W. P. C.: Two Cases of Phacogenetic Glaucoma with Anatomical Findings, Ophthalmologica **106**:136, 1943.

11. Bonavolonta, A.: Glaucoma Secondary to Hypermature Cataract, Rass. ital. otal. **19**:326, 1950.

12. Irvine, A. R., Jr., and Irvine, S. R.: Hypermature Cataract with Glaucoma, Tr. Pacific Coast Oto-Ophth. Soc. **31**:89, 1950.

13. Irvine, S. R., and Irvine, A. R.: Lens-Induced Uveitis, Am. J. Ophth. **35**:177, 370, 489, 1952.

14. Sugar, H. S.: Acute Secondary Glaucoma Due to Spontaneous Rupture of the Lens Capsule, Am. J. Ophth. **32**:1509, 1949.

15. Verhoeff, F. H., and Lemoine, A. N.: Hypersensitiveness to Lens Protein: Patient Desensitized and Successfully Operated on for Immature Cataract, Am. J. Ophth. **5**:700, 1922.

16. Cooper, S. N.; Lakhani, J. G., and Javer, B. N.: Proc. All-India Ophth. Soc. **9**:35, 1948.

17. Burky, E. L.: Experimental Endophthalmitis Phacoanaphylactica in Rabbits, Arch. Ophth. **12**: 536, 1934.

18. Müller, H.: Experimental Animal Investigation of Ophthalmia Phacogenetica, von Graefes Arch. Ophth. **153**:1, 1952.

19. Müller, H.: The Morphology of the Phacogenetic Reaction in Human Eyes, von Graefes Arch. Ophth. **154**:224, 1953.

20. Ballen, P. H., and Hughes, W. L.: Spontaneous Rupture of Lens Capsule, Am. J. Ophth. **39**:403, 1955.

21. Flocks, M. H.; Littwin, C. S., and Zimmerman, L. E.: Phacolytic Glaucoma, A. M. A. Arch. Ophth. **54**:37-45, 1955.

22. Pau, H.: Secondary Glaucoma Following Opening of Lens Capsule, Klin. Monatsbl. Augenh. **118**:600, 1951; abstracted, Excerpta Med. XII **6**: 115, 1952.

23. Heath, P.: Secondary Glaucoma Due to the Lens, Arch. Ophth. **25**:424, 1941.

24. Müller, H.: Clinical Picture and Histology of Phacogenetic Reaction, von Graefes Arch. Ophth. **155**:187, 1954.

25. Chandler, P. A., and Johnson, C. L.: A Neglected Cause of Secondary Glaucoma in Eyes in Which the Lens Is Absent or Subluxated, Arch. Ophth. **37**:740, 1947.

26. Barkan, O.: Glaucoma Secondary to Anterior Displacement of the Lens, Am. J. Ophth. **36**: 901, 1953.

27. McDonald, P. R., and Purnell, J. E.: The Dislocated Lens, J. A. M. A. **145**:220, 1951.

28. Alexander, R. L., and Kennedy, R. J.: Lens in Anterior Chamber of the Eye: Surgical Removal, Cleveland Clin. Quart. **20**:437, 1953.

29. Vogt, A.: A New Slit-Lamp Picture of Pupillary Control, Klin.Monatsbl. Augenh. **75**:1, 1925.

30. Vogt, A.: A New Slit-Lamp Picture: Exfoliation of the Anterior Lens Capsule as a Probable Cause of Senile Chronic Glaucoma, Schweiz. med. Wchnschr. **56**:413, 1926.

31. Irvine, R.: Exfoliation of the Lens Capsule (Glaucoma Capsulare), Am. J. Ophth. **23**:138, 1940.

32. Gradle, H. S., and Sugar, H. S.: Concerning the Chamber Angle: II. Exfoliation of the Zonular Lamella and Glaucoma Capsulare, Am. J. Ophth. **23**:982, 1940.

33. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. III, London, Henry Kimpton, 1940, pp. 3104-3111 and 3310.

34. Ross, R.: A Case of Acute Congestive Glaucoma with Exfoliation of Lens Capsule, Acta ophth. **27**:475, 1949.

35. Zavalia, J. M., and Ferrero, D. J.: Exfoliation of the Lens Capsule, Arch. oftal. Buenos Aires **25**:547, 1950.

36. Wilson, R. P.: Capsule Exfoliation and Glaucoma, New Zealand M. J. (Supp.) **52**:8, 1953.

37. Barkan, O.: A New Operation for Chronic Glaucoma, Am. J. Ophth. **19**:951, 1936.

38. Trantas, M.: Senile Lesions of the Anterior Lens Capsule and Pupillary Border, Arch. opht. **46**:482-491, 1929.

39. Theobald, G. D.: Pseudo-Exfoliation of Lens Capsule, Am. J. Ophth. **37**:1, 1954.

40. Weekers, L.; Weekers, R., and Dedoyard, J.: Pathogenesis of "Capsular" Glaucoma, Docum. ophth. **5-6**:555, 1951.

41. Weekers, L.; Weekers, R., and Dedoyard, J.: Mechanisms of Intraocular Hypertension in "Capsular" Glaucoma, Bull. Soc. belge opht. **95**:383, 1950.

42. Chandler, P. A.: Malignant Glaucoma, Tr. Am. Ophth. Soc. **48**:128-143, 1950.

43. Shaffer, R. N.: Role of Vitreous Detachment in Aphakic and Malignant Glaucoma, Tr. Am. Acad. Ophth. **58**:217, 1954.

44. Barkan, O.: Iridectomy in Narrow-Angle Glaucoma, Am. J. Ophth. **37**:504, 1954.

45. McDonald, P. R.: Malignant Glaucoma, A. M. A. Arch. Ophth. **51**:903, 1954.

46. Wegner, W.: Surgical Treatment of Malignant Glaucoma, Ber. deutsch. ophth. Gesellsch. **55**: 354, 1950.

47. Kronfeld, P. C., and McGarry, H. L.: Results of Surgical Treatment of Acute Congestive Glaucoma, Quart. Bull. Northwestern Univ. M. School **18**:203, 1944.

48. Sourdille, G. P.: Indications for Iridencleisis, Brit. J. Ophth. **34**:435, 1950.

49. Chandler, P. A.: Narrow-Angle Glaucoma, A. M. A. Arch. Ophth. **47**:695, 1952.

50. Haas, J. S., and Scheie, H. G.: Peripheral Iridectomy in Narrow Angle Glaucoma, Tr. Am. Acad. Ophth. **56**:589, 1952.

51. Goldmann, H.: Mode of Action of Iridectomy in Chronic Congestive Glaucoma, Ophthalmologica **123**:202, 1952.

52. Delmarcelle, Y.; Prijot, E., and Weekers, R.: Mode of Action, Indications, and Technique of Iridectomy, Bull. Soc. belge ophth. **105**:421-441, 1953.

53. Reese, A. B.: The Iridencleisis Operation for Glaucoma, Arch. Ophth. **34**:360, 1945.

54. Goldberg, H. K.: Operative Results in Acute Glaucoma, Am. J. Ophth. **34**:1376, 1951.

# Cervical Sympathetic Ganglionectomy and Aqueous Flow

ERIK LINNER, M.D., Uppsala, Sweden
and
EMILE PRIJOT, M.D., Liége, Belgium

The role of the sympathetic nervous system for the regulation of intraocular pressure has been studied by many investigators, with varied and contradictory results. Reviews of the literature have been made by Thiel,[11] Duke-Elder,[2] Magitot,[9] and, more recently, Jaffe[6] and Weinstein.[12] At the time of those studies attention was focused on intraocular pressure rather than on aqueous flow, since no suitable techniques for measurement of aqueous flow were available.

A change in the intraocular pressure of short duration can be caused by many different factors—for instance, a change in the blood volume of the eye. On the other hand, only three factors, namely, the rate of aqueous inflow, the facility of aqueous outflow, and the episcleral venous pressure, can determine the long-continued level of intraocular pressure.

The purpose of the present work was to study in rabbits the effect of extirpation of the superior sympathetic ganglion on the intraocular pressure and on the three factors, mentioned above, that are of importance for its permanent regulation. In order to allow the postoperative establishment of a steady state, no measurements were made earlier than one day following the operation.

Submitted for publication July 27, 1955.

From the Wilmer Ophthalmological Institute of The Johns Hopkins Hospital, Baltimore.

Present addresses: University of Uppsala (Dr. Linnér); Université de Liége (Dr. Prijot).

This study was supported in part by a grant from the Kellogg Foundation and in part by a training grant from the National Institute of Neurological Diseases and Blindness.

## MATERIAL AND METHODS

Male pigmented rabbits, weighing 2 to 2.5 kg., were used. The superior cervical ganglion on the right side was extirpated with the animal under general anesthesia (pentobarbital sodium, 65 mg/cc.; 0.5 ml/kg. body weight). Anatomically, the ganglion is an elongated structure extending posteriorly from just behind the common carotid artery. The ganglion is sometimes divided in two parts. A careful dissection is therefore necessary in order to make sure that the ganglion is completely removed. The intraocular pressure was measured by means of an electronic tonometer (V. Mueller), and Grant's[5] method of tonography was used according to the technique of Kornbluth and Linnér.[7] In this study, paraldehyde (1.5 cc/kg.) was given by stomach tube as a general anesthetic. The new tables of Friedenwald (1954)[3] were used for the calculations. The right eye was always examined before the left. The eyes were followed from 1 to 15 days after the operation. Since tonography could not be performed on the first day on account of the severe hypotension, the coefficient of facility of outflow was measured on that day on enucleated eyes according to the method described by Bárány.[1] Immediately after enucleation under pentobarbital anesthesia the two eyes were simultaneously perfused. A horizontal pipette containing a physiologically isotonic solution buffered with phosphate, pH 8, was connected to the anterior chamber by a 25-gauge needle. A constant pressure of 20 mm. Hg was exerted on the perfusion fluid by a water manometer.

The episcleral venous pressure was measured according to the method described by Linnér.[8]

## RESULTS

A. The following findings in the eye on the right (operation) side were observed on the first day after the extirpation of the ganglion.

1. In a group of 22 rabbits the mean intraocular pressure was 9.39±0.79 mm. Hg, as compared with 20.63±0.95 mm. Hg on the left (intact) side. Tonography could not be performed on the right eye because the intraocular pressure was so low that the instrument went off scale.

2. In 10 rabbits the episcleral venous pressure was found to be 9.10±0.29 mm. Hg in the right eye and 9.04±0.29 mm. Hg in the left eye. There was no statistically significant difference between the side of operation and the intact side in this respect. With an average intraocular pressure of 9.39 mm. Hg and an episcleral venous pressure of 9.10 mm. Hg, the average outflow pressure was close to zero.

3. In nine rabbits the coefficient of facility of outflow was measured after enucleation by means of the perfusion technique, described above. At a pressure of 20 mm. Hg no significant difference in the facility of outflow was found between the side of operation and the intact side (Table).

*Results of Extirpation of Right Cervical Superior Sympathetic Ganglion in Rabbits* *

| Time, Days | | Right Eye | | | Left Eye | | |
|---|---|---|---|---|---|---|---|
| | | $P_o$ | $C$ | $F$ | $P_o$ | $C$ | $F$ |
| 1 | $m$..... | 9.39 | 0.209† | .... | 20.63 | 0.250† | .... |
| | $\sigma$..... | 0.79 | 0.022 | .... | 0.95 | 0.024 | .... |
| | $n$..... | 22 | 9 | .... | 22 | 9 | .... |
| 2 | $m$..... | 20.20 | 0.220 | 2.53 | 19.48 | 0.206 | 2.16 |
| | $\sigma$..... | 1.51 | 0.016 | .... | 1.26 | 0.014 | .... |
| | $n$..... | 16 | 12 | .... | 16 | 11 | .... |
| 3-5 | $m$..... | 22.06 | 0.264 | 3.48 | 20.40 | 0.280 | 3.19 |
| | $\sigma$..... | 1.31 | 0.017 | .... | 1.19 | 0.023 | .... |
| | $n$..... | 15 | 14 | .... | 15 | 14 | .... |
| 7-10 | $m$..... | 21.87 | 0.293 | 3.77 | 18.89 | 0.294 | 2.94 |
| | $\sigma$..... | 1.71 | 0.046 | .... | 1.65 | 0.019 | .... |
| | $n$..... | 10 | 9 | .... | 10 | 7 | .... |
| 13-15 | $m$..... | 20.49 | 0.299 | 2.99 | 19.17 | 0.279 | 2.84 |
| | $\sigma$..... | 1.70 | 0.024 | .... | 1.08 | 0.021 | .... |
| | $n$..... | 12 | 9 | .... | 12 | 9 | .... |

* $P_o$ indicates intraocular pressure, in millimeters Hg; $C$, facility of outflow, cu. mm./min./mm. Hg; $F$, flow of aqueous, cu. mm./min., calculated from the mean values for $P_o$ and $C$; $m$, arithmetic mean; $\sigma$, standard error of the mean; $n$, number of eyes.

† $C$ determined by perfusion after enucleation on first day only; all others, by tonography.

B. On the second postoperative day the intraocular pressure was restored to normal in practically all cases. On this day the rate of aqueous flow and the facility of outflow were slightly decreased in both eyes. The significance of this transitory finding remains obscure. There was no statistically significant difference between the two eyes at this time. The intraocular pressure was then followed up to 15 days after operation, and tonography was performed at varying intervals (Table).

## COMMENT

On the first day after operation the intraocular pressure on the side of operation was, on the average, reduced to the level of the episcleral venous pressure. The facility of outflow measured by perfusion after enucleation did not show any significant difference between the eye on the side of operation and the intact side. An outflow pressure close to zero without evidence for an infinite increase in the facility of outflow indicates a markedly decreased rate of aqueous flow.

The suppression of aqueous flow one day following ganglionectomy suggests that an adrenergic mechanism may be involved in the intraocular secretory process. Friedenwald and Buschke [9] (1941) have, in fact, shown that certain aspects of the secretory mechanism are inhibited by adrenalectomy and reestablished by administration of very small doses of epinephrine. They reported no effect of preganglionic sympathectomy but did not perform a ganglionectomy in their experiments.

In the present experiments the intraocular pressure, the facility of aqueous outflow, and the rate of aqueous flow all were restored to normal by the third postoperative day. The values found after restoration are in good agreement with the results of similar determinations on the normal eyes of another group of rabbits under the same general anesthesia (Stone and Prijot [10]).

In a similar study now in progress concerning the effect of preganglionic cervical sympathectomy, no marked effect on the intraocular pressure or aqueous flow has been found so far.

SUMMARY

The effect of extirpation of the superior cervical sympathetic ganglion on the aqueous humor dynamics was studied in rabbits. A marked decrease of the intraocular pressure and of the rate of aqueous flow was found one day after the operation, followed by a restoration to normal values a few days later. No significant change was found in the facility of outflow or in the episcleral venous pressure.

REFERENCES

1. Bárány, E. H.: In Vitro Studies of the Resistance to Flow Through the Angle of the Anterior Chamber, Acta Soc. med. upsalien. **59**:260, 1953.

2. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. I, St. Louis, C. V. Mosby Company, 1942, p. 531.

3. Friedenwald, J. S.: Standardization of Tonometers, Decennial Report by the Committee on Standardization of Tonometers, American Academy of Ophthalmology and Otolaryngology, 1954, Chap. VII.

4. Friedenwald, J. S., and Buschke, W.: Role of Epinephrine in the Formation of the Intraocular Fluid, Am. J. Ophth. **24**:1105, 1941.

5. Grant, M. W.: Tonographic Method for Measuring the Facility and Rate of Aqueous Flow in Human Eyes, Arch. Ophth. **44**:204, 1950.

6. Jaffe, N. S.: Sympathetic Nervous System and Intraocular Pressure, Am. J. Ophth. **31**:1597, 1948.

7. Kornbluth, W., and Linnér, E.: Experimental Tonography in Rabbits, A. M. A. Arch. Ophth. **54**:717, 1955.

8. Linnér, E.: The Outflow Pressure in Normal and Glaucomatous Eyes, Acta ophth. **33**:101, 1955.

9. Magitot, A.: La Tension oculaire, in Bailliart, P.; Coutela, C.; Redslob, E., and Velter, E.: Traité d'ophtalmologie, Paris, Masson & Cie, 1939, Vol. II, p. 137.

10. Stone, H., and Prijot, E.: Effect of a Barbiturate and Paraldehyde on Aqueous Humor Dynamics, A. M. A. Arch. Ophth. **55**:834, 1955.

11. Thiel, R.: Die Physiologie und Pathologie des Augendruckes, in Schieck, F., and Brückner, A., Editors: Kurzes Handbuch der Ophthalmologie, Vol. IV, Berlin, Springer-Verlag, 1931, p. 666.

12. Weinstein, P.: Nervism in Ophthalmology, Ophthalmologica **127**:164, 1954.

# The Effect of a Barbiturate and Paraldehyde on Aqueous Humor Dynamics in Rabbits

HOWARD H. STONE, M.D., Baltimore
and
EMILE L. PRIJOT, M.D., Liége, Belgium

In a previous study from this laboratory, Kornbluth and Linnér [1] demonstrated the possibility and utility of tonography in rabbits. Their experiments were performed under barbiturate (pentobarbital [Nembutal]) anesthesia. Subsequently, Becker and Constant [2] showed that tonography could be successfully performed on these animals with topical anesthesia only. The purpose of the present study was to find out whether, and to what extent, general anesthesia induces changes in the dynamics of the aqueous humor. To this end we have measured the coefficient of facility of outflow ($C$), the rate of aqueous flow ($F$), the episcleral venous pressure ($P_v$), and the ocular rigidity ($K$) in normal rabbits with and without general anesthesia. In view of the large variation in response of different species to anesthetic drugs, the reader is cautioned against assuming that the results found in rabbits necessarily apply to man.

The effects of general anesthesia on intraocular pressure have been previously studied by several investigators. Rubino and Esente [3] reported that barbiturates lowered intraocular pressure (I. O. P.) by "paralysis" of the diencephalon. Schmerl and Steinberg [4] believed that paraldehyde anesthesia primarily affected the cerebral cortex and produced no changes in ocular tension, whereas pentobarbital (Nembutal) sodium anesthesia, which they assumed to act predominantly on the diencephalon, produced a slight decrease in I. O. P.

The mechanism by which a control of I. O. P. was mediated has long been an intriguing problem. Magitot,* Beauvieux,[7] Weinstein,[8] Thiel,[9] and von Sallmann and Loewenstein [10] implicated the central and/or autonomic nervous system.

## METHODS AND MATERIALS

A total of 78 rabbits were used in these experiments. The animals were pigmented male rabbits weighing between 2.2 and 3.0 kg.† The animals were on a regular "Sherwood-Feed" pellet diet and water ad lib.

*Tonography.*—Tonograms were obtained on rabbits by the method described by Kornbluth and Linnér.[1] An electronic Schiøtz tonometer (V. Mueller) connected with a recorder (Minneapolis Honeywell-Brown electronic potentiometer) was used both for tonography and for tonometry.

*Fluorescein-Appearance Time.*—For determinations of fluorescein-appearance time, 2.5 cc. of fluorescein sodium (Fluorescite) ‡ was injected intravenously into the rabbit's ear over a period of 10 seconds. This method was developed by Linnér and Friedenwald.§ For observations of the dye in the

Received for publication Aug. 1, 1955.

From the Wilmer Ophthalmological Institute of The Johns Hopkins University and Hospital, Baltimore.

This work was supported by a grant from the W. H. Kellogg Foundation, and in part by a Training Grant from the National Institute of Neurological Diseases and Blindness and in part by a gift from the American Cyanamid Company.



* References 5 and 6.

† Purchased from Research Supply Co., Philadelphia.

‡ C. F. Kirk Co., New York.

§ Linnér, E., and Friedenwald, J. S., in Symposium on Diamox in Ophthalmology, report presented at the Wilmer Residents' Meeting, Baltimore, April 2, 1954.

pupil, a Haag-Streit ocular biomicroscope (slit lamp) was used. The same observer made repeated observations in the same group of animals. Eight seconds from the beginning of the injection was estimated as the average circulation time.

*Anesthetics.*—Three major types of experiments were carried out:

1. Pentobarbital Sodium: One-third of the rabbits were anesthetized by the intravenous injection of 0.5 cc. per kilogram of body weight of a solution containing 65 mg. of pentobarbital per cubic centimeter of 10% alcohol. This dose produced moderate to deep narcosis.[11] Tonometric determinations of I. O. P. were made on one eye, beginning six minutes after sleep was induced, and were repeated at approximately 5-minute intervals for 40 minutes after the anesthetic was given. At approximately 45 minutes tonography was performed on the same eye. One drop of 0.5% Ophthaine‖ (2-diethylaminoethyl-3-amino-4-propoxybenzoate hydrochloride) was instilled into the conjunctival sac before tonometry and tonography.

2. Paraldehyde (100%): One-third of the rabbits were anesthetized by gastric intubation with paraldehyde,¶ 1.5 cc. per kilogram of body weight, mixed 1:7 with tap water. Since the time of induction varied from animal to animal, all tonometric determinations were begun only 30 minutes after the anesthetic had been introduced into the stomach. At this time all animals were in moderate to deep narcosis. The I. O. P. was determined tonometrically every 5 minutes up to 65 minutes from the time the anesthetic was introduced. At 70 minutes tonography was performed. One drop of Ophthaine was instilled into the conjunctival sac before tonometry and tonography.

3. Topical Anesthesia Without General Anesthesia: Approximately one-third of the rabbits served as controls and did not receive general anesthesia. One drop of Ophthaine was instilled into the conjunctival sac before tonometry and tonography.

Comparative Ratios: Ten rabbits were selected for comparative-ratio studies (Table 2). This group of animals was subjected on successive weeks to tonography under pentobarbital sodium anesthesia, under paraldehyde anesthesia, and without general anesthesia. The order in which the experiments were performed on a given animal was varied in different animals so as to allow the possibility of irreversible changes in the eye after repeated tonographic readings and/or repeated general anesthesia.

‖ E. R. Squibb & Sons.

¶ References 4 and 11.

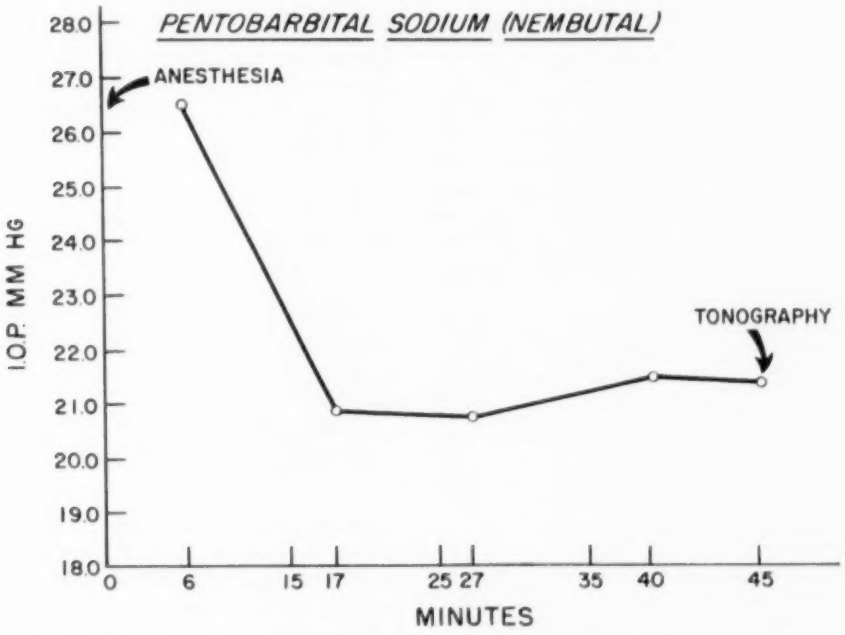



Fig. 1.—Mean intraocular pressures during pentobarbital (Nembutal) sodium anesthesia in 13 rabbits.

*Episcleral Venous Pressure* ($P_v$).—This was determined, under various conditions, by the method described by Linnér.[12]

*Ocular Rigidity* (K).—This was determined by comparing successive tonometric readings with the 5.5 and 10.0 gm. weights, using the 5.5-gm. weight first. Friedenwald's tables[13] were used for computations.

The coefficient of the facility of outflow ($C$) was calculated from the tonograms by the methods described by Grant.# The rate of aqueous flow was calculated by the equation $F=C\ (P_o-P_v)$.

## RESULTS

*Pentobarbital Sodium.*—In Figure 1, each point plotted on the graph represents (*a*) the average of several determinations of I. O. P. for each animal according to the following time schedule: at 6 minutes, between 15 and 25 minutes, between 26 and 35 minutes, and from 36 minutes on, and (*b*) the over-all mean for the figures determined under (*a*) for 13 animals. Thus, the five points plotted in Figure 1 represent the average values of over 200 determinations of I. O. P.

As can be seen from Figure 1, the I. O. P. falls during the first 15 minutes and then reaches a fairly straight plateau.* During the period represented by the plateau the flow of aqueous can be assumed to have been in a steady state. As depicted on the graph, tonography was performed during a period of steady state.

TABLE 1.—*Mean Coefficient of Facility of Outflow (C) and Mean Intraocular Pressure During Steady State* *

| Anesthetic | No General Anesthesia | Pentobarbital Sodium | Paraldehyde |
|---|---|---|---|
| Coefficient of facility of outflow ($C$), cu. mm./min./mm. Hg | 0.24±0.012 | 0.33±0.030 | 0.29±0.023 |
| Intraocular pressure, mm. Hg | 23.0±1.23 | 19.7±1.84 | 20.8±1.90 |

* The same 10 rabbits were used under all these conditions.

TABLE 2.—*Mean of Ratios of C and Intraocular Pressure for Pentobarbital-No General Anesthesia and Paraldehyde-No General Anesthesia Obtained from Group of Ten Rabbits Shown in Table 1*

| Mean Ratio | Pentobarbital Sodium | Paraldehyde |
|---|---|---|
| | No General Anesthesia | No General Anesthesia |
| Coefficient of facility of outflow ($C$) | 1.39±0.12 | 1.23±0.09 |
| Intraocular pressure | 0.855±0.058 | 0.899±0.047 |

TABLE 3.—*Comparison of Mean Coefficient of Facility of Outflow in Two Groups of Rabbits ($p<0.10$)*

| Anesthetic | Pentobarbital Sodium | Paraldehyde |
|---|---|---|
| Coefficient of facility of outflow ($C$), cu. mm./min./mm. Hg | 0.313±0.020 | 0.276±0.013 |
| No. of animals | 16 | 22 |

TABLE 4.—*Aqueous Flow (F) During General Anesthesia as Compared with Flow Without General Anesthesia* *

| Method | No General Anesthesia | Pentobarbital Sodium | Paraldehyde |
|---|---|---|---|
| Mean $F$, cu. mm./min.† (tonography) | 3.30 | 3.48 | 3.39 |
| Fluorescein-appearance time, sec.‡ (relative flow) | 63±6.2 n = 15 | 64±7.7 n = 15 | 61±7.5 n = 14 |

* All values were obtained during steady state.
† Refers to the group of 10 rabbits reported in Tables 3 and 4. $F$ was calculated by multiplying $C$ by $(P_o-9.0)$.
‡ Values refer to different groups of rabbits.

TABLE 5.—*Episcleral Venous Pressure During General Anesthesia*

| | Pentobarbital Sodium | Paraldehyde |
|---|---|---|
| Episcleral venous pressure ($P_v$),* mm. Hg | 9.4±0.24 n = 6 | 9.8±0.14 n = 6 |
| Mean ratios of ocular rigidity † ($K$) | 0.92±0.046 n = 13 | 0.92±0.058 n = 12 |

* Measurements made on the same six eyes under both anesthetics.
† Estimates of mean ratios of ocular rigidity with general anesthesia relative to measurements on the same eyes without general anesthesia. The figures give the ratios of the paired measurements, not the absolute values of the measurements.

*Paraldehyde.*—In Figure 2, each point plotted on the graph represents (*a*) the average of several determinations of I. O. P. for each animal according to the following time schedule: at 30 minutes, between 35 and 45 minutes, between 46 and 55 minutes,

# References 14 and 15.

* There may be an initial transitory rise of I. O. P. under this anesthetic, since the six-minute reading yielded an average pressure slightly higher than that found without general anesthesia.

and between 56 and 70 minutes, and (*b*) the over-all mean for the figures determined under (*a*) for 10 animals. As in the case of pentobarbital anesthesia, tonography was performed during a period of steady state.

*Intraocular Pressure* (I. O. P.) *and Coefficient of Facility of Outflow* (C).—The results are summarized in Tables 1, 2, and 3. The mean and the standard error of the mean, as well as the number of animals used, are given in each Table. Tables 1 and 2 refer to the results obtained in the same group, of 10 animals. Table 2 shows the ratios obtained by comparing the same group of eyes with general anesthesia with the values obtained without general anesthesia. Table 3 refers to two different groups of rabbits under two different anesthetics. Tonometry and tonography were always performed on the same eye.

*Aqueous Flow* (F).—In Table 4 the results are presented for the rate of aqueous flow obtained by tonography and fluorescein-appearance time. Both procedures showed no change in the rate of flow of the aqueous under the conditions compared.

*Episcleral Venous Pressure and Ocular Rigidity.*—The results are summarized in Table 5 and will be discussed below.

## COMMENT

The data presented above were calculated on the assumption that the tables of tonometry, tonography, and ocular rigidity employed for human eyes may, in general, be applied to rabbit eyes with reasonable reliability. According to the work of Kornbluth and Linnér,[1] such an assumption could be considered valid. Moreover, in comparing the tonographic determinations on the same eye under different experimental conditions, systematic errors tend to cancel out.

*Controls.*—There were several controls in the experiments described. First, all studies under general anesthesia were carried out twice, i. e., under pentobarbital sodium and under paraldehyde. Second, a group of control animals was studied without general anesthesia in otherwise identical circumstances. Third, a group of 10 animals was studied successively under all three conditions: pentobarbital sodium, paraldehyde, and without general anesthesia. The values obtained for their eyes under general anesthesia were compared with the same set of eyes without general anesthesia (Mean Ratios, Table 2). Fourth, the sequence in which the general-anesthesia experiments were performed was changed in different groups in order to take into account possible irreversible ocular changes secondary to general anesthesia and/or repeated tonography on the same eye. No evidence was found to substantiate this assumption. Fifth, aqueous flow was determined by two independent methods: tonography and fluorescein-appearance time. The results were in good agreement.

*Anesthetics.*—Pentobarbital Sodium: This drug appears to act centrally.[11] In large doses, it is a respiratory depressant and lowers blood pressure by peripheral vasodilatation. It is a short-acting barbiturate, and after a single narcosis-inducing dose the rabbit usually recovered from the anesthesia after about one hour. A steady state does not exist in the first 15 to 20 minutes (Fig. 1) and is also very unlikely to exist shortly before awakening from the anesthesia. Thus, one is dealing with a relatively short period (between 20 and 40 minutes following the injection) of steady state. Laryngospasm was encountered rather frequently with this anesthetic.

Paraldehyde: Here the situation is somewhat different. This drug is not a barbiturate, and laryngospasm was rarely seen. By the time 30 minutes after gastric intubation had elapsed, all rabbits were in a long-lasting (eight hours), quiet, deep narcosis. As will be seen from Figure 2, the I. O. P. remains relatively constant during the first hour; i. e., fluctuations of tension were less than 2.0 mm. Hg.

Topical Anesthesia (without general anesthesia): In spite of some of the obvious

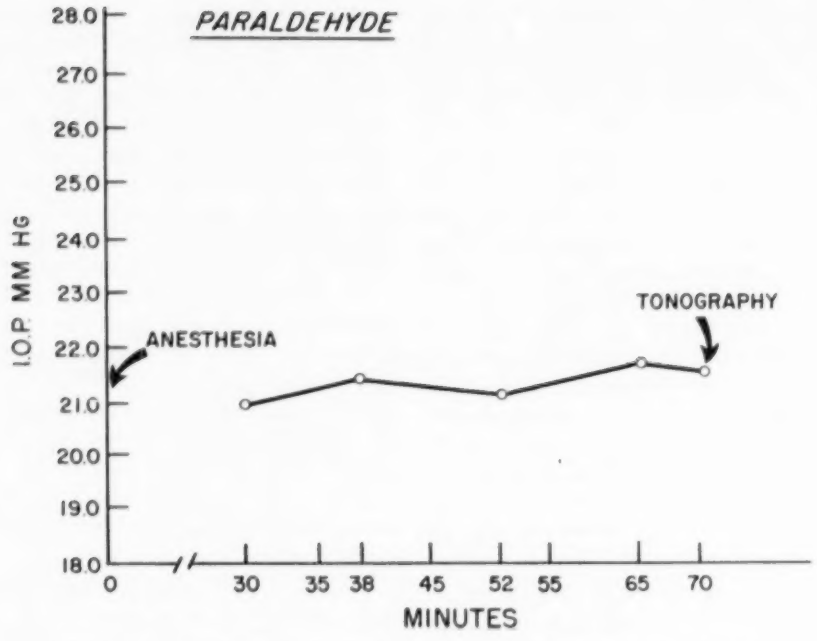



Fig. 2.—Mean intraocular pressures during paraldehyde anesthesia in 10 rabbits.

disadvantages of general anesthesia, the study of aqueous humor dynamics without general anesthesia is also fraught with certain hazards. If the animal is excited, it is not only extremely difficult to obtain reliable tonographic and tonometric measurements but in addition the dynamics of the aqueous humor per se may be altered. Careful wrapping of the animal in a towel and the avoidance of sudden, jerky movements in handling the animal, together with the avoidance of any painful stimuli, are necessary for successful tonography without general anesthesia.

Intraocular Pressure: As can be seen from Figure 1 and Tables 1 and 3, the I. O. P. under pentobarbital and paraldehyde anesthesia is lower than the values found with topical anesthesia alone. Under pentobarbital the I. O. P. fell during the first 15 to 20 minutes. In a separate group of 10 rabbits tested both under general and without general anesthesia, the mean ratio of I. O. P. for pentobarbital sodium-no general anesthesia was $0.855 \pm 0.058$. This difference is statistically significant ($p < 0.03$). The I. O. P. under paraldehyde was also found to be lower than the values obtained without general anesthesia. The mean ratio was $0.890 \pm 0.047$ ($p < 0.05$).

*Episcleral Venous Pressure* ($P_v$).—As shown in Table 5, the $P_v$ under pentobarbital anesthesia is essentially the same as that under paraldehyde anesthesia. The values obtained are in close agreement with those reported by Seidel [16] in rabbits without general anesthesia. His figure was an average of 9.0 mm. Hg. Linnér [12] reported the value of $8.97 \pm 0.17$ mm. Hg in rabbits under pentobarbital sodium anesthesia.

*Ocular Rigidity* (K).—In Table 5 the results of a comparison of the ocular rigidity under general anesthesia and that without general anesthesia are presented in the form of mean ratios of ocular rigidities for pentobarbital-no general anesthesia and paraldehyde-no general anesthesia, respectively. As can be seen, these ratios are not significantly different from unity. Therefore, neither of

these two anesthetics has a significant effect on ocular rigidity.

*Rate of Aqueous Flow* (F).—As shown in Table 4, aqueous flow with general anesthesia is essentially the same as that without general anesthesia. This appeared true whether flow was estimated by means of tonography or by fluorescein-appearance time (relative flow).

*Coefficient of Facility of Outflow* (C).—The most striking finding of the data reported here is an increase of *C* under pentobarbital and paraldehyde anesthesia as compared with values obtained without anesthesia. From Table 2 it is apparent that in the same group of animals, when values for the same eyes under general anesthesia are compared with values obtained without general anesthesia, the *C* is found to be larger with general anesthesia. The mean of the ratio pentobarbital sodium-no general anesthesia is $1.39 \pm 0.12$, which is significantly greater than unity ($p = 0.02$). For paraldehyde-no general anesthesia the ratio is $1.23 \pm 0.09$ ($p < 0.05$). The data are insufficient to determine whether the difference between pentobarbital sodium and paraldehyde anesthesia is significant.

This is not the first time that it has been shown that the coefficient of the facility of outflow (or the resistance to aqueous outflow) was not a stable or fixed entity. Grant,[14] Prijot and Weekers,[17] and Becker and Friedenwald[18] reported that pilocarpine increased the *C*. Bárány and Scotchbrook[19] were able to show that the resistance to outflow could be reduced by the enzyme hyaluronidase. Hoover ‡ demonstrated that the *C* changed with pregnancy and during the menstrual cycle, and recently Kornbluth and Linnér[1] showed that in rabbits *C* decreased after carotid artery ligation.

This study casts no light on the physiological mechanism by which the general anesthetics influence facility of aqueous outflow. However, most of the pharmacological effects of barbiturates and paraldehyde are considered the results of centrally located actions of these drugs. The assumption is therefore strong that the effect on aqueous outflow is also via the central or the autonomic nervous system. A corollary to this assumption is that the central control of intraocular pressure operates at least in part through control of the aqueous outflow mechanism.

‡ Hoover, R. E.: Personal communication to the authors, 1955.

## SUMMARY AND CONCLUSIONS

Factors concerned in the dynamics of the aqueous humor in rabbits were studied under (1) pentobarbital (Nembutal) sodium anesthesia, (2) paraldehyde anesthesia, and (3) without general anesthesia.

Under the general anesthetics used there was a fall in intraocular pressure associated with an increased facility of outflow of aqueous humor. This effect tended to be more marked under pentobarbital sodium anesthesia, a barbiturate. No measurable changes occurred in the rate of aqueous flow, in ocular rigidity, or in episcleral venous pressure.

When studies on aqueous dynamics, requiring steady-state conditions, are carried out under general anesthesia, special precautions as to timing are necessary to insure that conditions of steady state exist.

Dr. Jonas S. Friedenwald gave advice and criticism. Dr. Erik Linnér made the determinations of episcleral venous pressure.

Wilmer Ophthalmological Institute (Dr. Stone).

Clinique Ophthalmologique, Université de Liége (Dr. Prijot).

## REFERENCES

1. Kornbluth, W., and Linnér, E.: Experimental Tonography in Rabbits, A. M. A. Arch. Ophth. **54**:717, 1955.

2. Becker, B., and Constant, M. A.: Experimental Tonography: Effect of the Carbonic Anhydrase Inhibitor Acetazoleamide on Aqueous Flow, A. M. A. Arch. Ophth. **54**:321, 1955.

3. Rubino, A., and Esente, J.: Occhio e diencefalo, Riv. oto-neuro-oftal. **25**:351, 1950.

4. Schmerl, E., and Steinberg, B.: Role of the Diencephalon in Regulating Ocular Tension, Am. J. Ophth. **31**:155, 1948.

5. Magitot, A.: Les voies nerveuses directes reliant la rétine à l'hypothalamus, Ann. ocul. **182**: 569, 1949.

6. Magitot, A.: Tension oculaire et diencéphale, Bull. Soc. opht. France, p. 603, 1949.

7. Beauvieux, J.: Œil et diencéphale, Bull. Soc. opht. France, p. 567, 1949.

8. Weinstein, P.: Nervism in Ophthalmology, Ophthalmologica **127**:164, 1954.

9. Thiel, R.: Die medikamentöse Therapie des primären Glaukoms, Klin. Monatsbl. Augenh. **125**: 513, 1954.

10. von Sallmann, L., and Loewenstein, O.: Responses of Intraocular Pressure, Blood Pressure and Cutaneous Vessels to Electric Stimulation in the Diencephalon, Am. J. Ophth. **39**:11 (April, Pt. II), 1955.

11. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, Ed. 2, The Macmillan Company, 1955.

12. Linnér, E.: The Outflow Pressure in Normal and Glaucomatous Eyes, Acta ophth. **33**:101, 1955.

13. Friedenwald, J. S.: Calibration of Tonometers, Decennial Report by the Committee on Standardization of Tonometers, American Academy of Ophthalmology and Otolaryngology, 1954, Chap. VII.

14. Grant, W. M.: Tonographic Method for Measuring the Facility and Rate of Aqueous Flow in Human Eyes, Arch. Ophth. **44**:204, 1950.

15. Grant, W. M.: Clinical Measurements of Aqueous Outflow, A. M. A. Arch. Ophth. **42**:113, 1951.

16. Seidel, E.: Über die Messung des Blutdruckes in dem episcleralen Venengeflecht, den vorderen Ciliar- und den Wirbenvenen normaler Augen, von Graefes Arch. Ophth. **112**:252, 1923.

17. Prijot, E., and Weekers, R.: Mode d'action de la pilocarpine dans le glaucome chronique non-inflammatoire, Ophthalmologica **124**:12, 1952.

18. Becker, B., and Friedenwald, J. S.: Clinical Aqueous Outflow, A. M. A. Arch. Ophth. **50**:556, 1953.

19. Bárány, E. H., and Scotchbrook, S.: Influence of Testicular Hyalurondiase on the Resistance to Flow Through the Angle of the Anterior Chamber, Acta physiol. scandinav. **30**:240, 1954.

# Electroretinography in Night Blindness and Other Vitamin-A Deficiencies

R. P. DHANDA, M.B., M.S., D.O., Indore, India

An extinguished electroretinogram in cases of retinitis pigmentosa has been demonstrated by Prof. G. Karpe, of Sweden. Lorrin A. Riggs (1954) and Armington and Schwab (1954) have reported similar electroretinographic responses in cases of congenital night blindness and retinitis pigmentosa.

This paper deals with yet another form of night blindness and its effects on the human electroretinogram. As is well known, an adequate vitamin A level in the blood is mainly responsible for the normal functioning capacity of the rods. Similarly, the scotopic electroretinographic tracing represents the electrical response of the rods. A direct relationship may thus exist between the clinical manifestations of vitamin A deficiency and the electroretinogram.

The height of the b-wave of an electroretinogram of a dark-adapted eye represents directly the functioning capacity of the rods and indirectly the grade of vitamin A deficiency in the blood. This paper indicates the relationship between (1) clinical manifestations of vitamin A deficiency, (2) the vitamin A level in the blood, and (3) the electrical response of a dark-adapted retina.

## PRESENT INVESTIGATION

The present investigation is based on the following fundamental facts:

An adequate supply of vitamin A is essential for the normal functioning of rods. The chemical and physical changes that take place in the rods when stimulated are consequently dependent on proper supply of nutrition. Stimulation of the retina by light results in the development of electric potential at the level of its cellular elements. Therefore, the electrical response of the retina of a dark-adapted eye will be materially affected if the nutrition and function of the rods are appreciably diminished.

The purpose of these investigations, therefore, has been (1) to record the action potential of the retina in normal Indians; (2) to study the variations in the electrical response in subjects with vitamin A deficiency, e. g., patients suffering from xerosis alone and from xerosis with night blindness, and (3) to study the effect of administration of vitamin A on the clinical and electrical phenomena in these deficiency states.

### METHOD FOR CLINICAL RECORDING OF ELECTRORETINOGRAM

The method adopted in this investigation is exactly the same as that used by Professor Karpe, of Sweden, with one exception, i. e., that the amplifier used here has a sensitivity in which 1 mv. equals 1 cm., instead of 1 mv. equaling 2 cm., as in the case of Professor Karpe's amplifier. Figure 1 shows a subject prepared for the investigation and the apparatus used.

The standard illumination of a flash stimulus is 80 luxes, measured with a lux meter before each eye is studied. The stimulus lasts one-fourth second; the machine used is the Sanborn electrocardiograph machine, and stimuli are repeated at intervals of 15 seconds. Depending upon the cooperation of the patient, 12-15 tracings are recorded for each eye. A fasting sample of blood is collected the same morning, and its vitamin A content is analyzed by the antimony trichloride method on a Lumetron photoelectric colorimeter.

Recorded for publication Aug. 30, 1955.

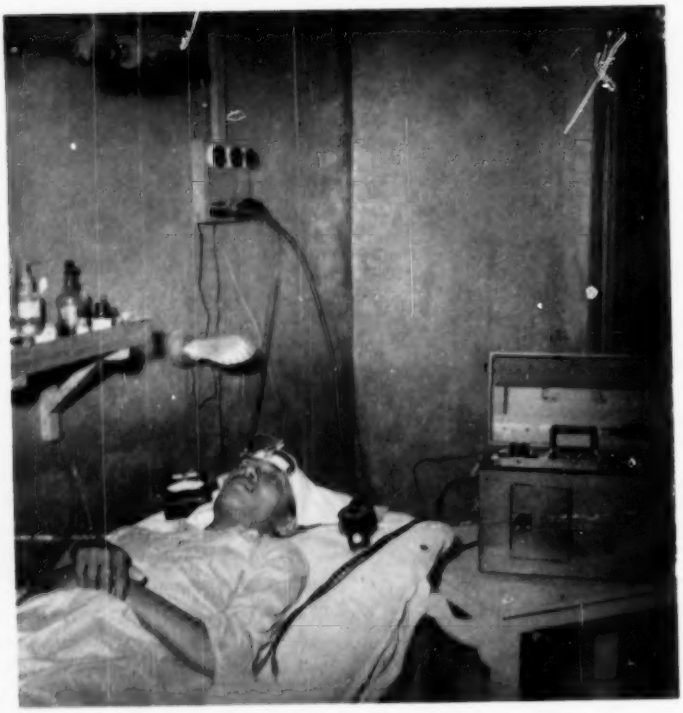


Fig. 1.—Photograph showing subject prepared for investigation and the apparatus used.

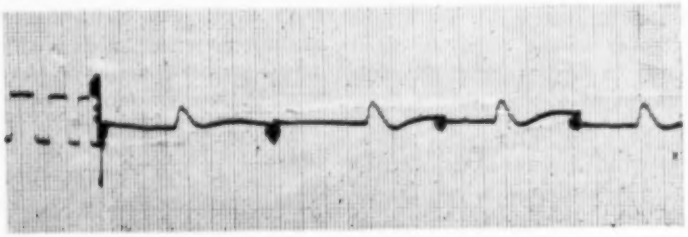


Fig. 2.—Normal electroretinogram.

The patients are given massive vitamin A injections (Unichem Laboratory, India) every fourth day I. M.; clinical improvement is noted, and electroretinographic examinations are repeated at intervals.

## Results

*Electroretinogram in Normal Adults.*—An electroretinogram could be obtained from 35 eyes of 22 persons past the age of 15 years, although cooperation varied. Electroretinograms of 19 eyes of 11 persons were taken for normal averages because the patients were absolutely steady and the height of the b-wave could be unmistakably and accurately measured.

The average b-potential of 19 eyes of 11 Indian adults was 0.32 mv. and a typical electroretinogram of a medical student is shown in Figure 2.

A curious feature noted has been the varying types of extraneous electric potentials immediately following the b-wave in the less cooperative patients. Each individual subject has his own type of disturbance, which remains the same after each flash stimulus.

In Figure 3 is illustrated a few disturbances observed among the patients of low-standard cooperation.

Estimation of the vitamin A level of the plasma was done in 12 cases. The results are an average of 150 I. U. per 100 cc. of plasma, with a maximum of 194 I. U. in one case and a minimum of 103 I. U. in another.

*Electroretinogram in Normal Children.*—These subjects were studied in two groups: (1) children between the ages of 7 and 15 years, and (2) children below the age of 7 years.

Between Ages of 7 and 15 Years: An electroretinogram could be recorded in a very large percentage of children past the age of 7 years without a general anesthesia. Twenty-six eyes of normal children of all grades of social and economic status were studied, but the results for children with very good cooperation are taken for averages. The average b-potential of 11 eyes of 8 children between the ages of 7 and 15 years was 0.31 mv., with an average vitamin A content of 39 I. U. per 100 cc. of plasma, with a maximum of 96 I. U., and a minimum of 8.5 I. U.

Below the Age of 7 Years: General anesthesia was necessary and the average b-potential of eight eyes of six children below the age of 7 years was 0.26 mv., with an average vitamin A content of 26 I. U. per 100 cc.

Fig. 3.—Electroretinograms showing extra potentials immediately following the b-wave: Left, the negative type; middle, the positive type, and, right, the reduplication type. Note that the height of the b-wave can be accurately measured in each case.

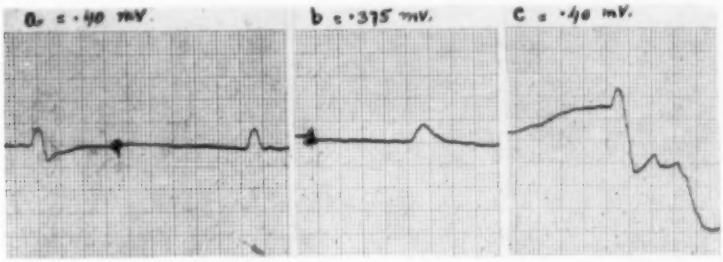



Fig. 4.—Left (0.40 mv.), before anesthesia; middle (0.375 mv.), patient under general anesthesia; right (0.40 mv.), during stage of recovery.

Note the broad-based ERG taken with the patient under general anesthesia. This has been observed as a usual feature of the ERG with general anesthesia, but the height of the b-potential is practically unchanged.

In Figure 4 is shown an electroretinogram recorded without and one with general anesthesia in an 11-year-old child.

*Electroretinograms in Cases of Clinical Manifestations of Vitamin A Deficiency.*—Xerosis: An investigation of 56 eyes of 36 adults was made, and 39 eyes of 27 children were similarly examined. Here, again, the same procedure of giving general anesthesia to children below the age of 7 years was adopted.

The average b-potential for 16 eyes of 11 adults with very good cooperation and xerotic patches of more than 3 mm. in diameter was 0.290 mv., the average vitamin A content of 8 of these persons being 103 I. U. per 100 cc. of plasma, with a maximum of 185 I. U. and a minimum of 10 I. U., per 100 cc.

The average b-potential of nine eyes of six children above the age of 7 years, again with the same grade of xerosis, was 0.24 mv., the average vitamin A content being 32 I. U. per 100 cc. of plasma.

Under the age of 7 years, 16 eyes of 11 children under general anesthesia were examined. Of these children, the electroretinogram was completely extinguished in five. The average b-potential of the other six children was 0.18 mv. The average vitamin A content for this age group was 20 I. U. per 100 cc. of plasma.

Figure 5 illustrates three cases of xerosis of long duration in adults in whom neither the electroretinogram nor the vitamin A content of the blood was materially altered.

Figure 6 shows the electroretinogram of two children with xerosis alone.

Night Blindness: Night blindness due to vitamin A deficiency is comparatively less common in the adult age groups. Eleven persons were examined, all of whom had clinically apparent patches of xerosis over the conjunctiva and complained of night blindness of not more than two months' duration. Of the 19 eyes of these patients, the electroretinogram was completely extinguished in 13; 5 eyes had a potential of less than 0.05 mv., and only one eye had a potential of 0.125 mv.

Among the children, night blindness associated with xerosis was a very common clinical feature. Xerosis may last for years in adults, without night blindness, but most of the children with xerosis, if untreated, very soon develop night blindness.

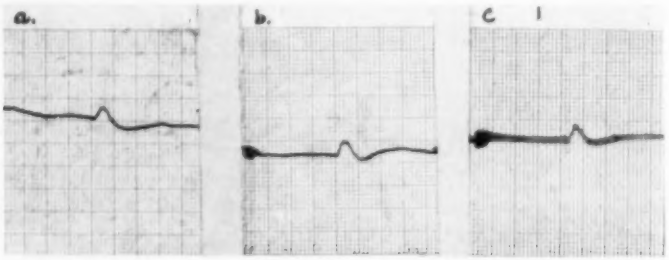



Fig. 5.—Left, Miss V. B., aged 17 years; xerosis 2+, of five years' duration; b-potential, 0.25 mv.; no night blindness. Middle, S. Z., aged 24 years; xerosis 2+; b-potential 0.30 mv.; vitamin A content 136 I. U. per 100 cc. of plasma; no night blindness. Right, Mrs. C. M., aged 29 years; xerosis 2+; b-potential 0.275 mv.; vitamin A content 130 I. U. per 100 cc. plasma; no night blindness.

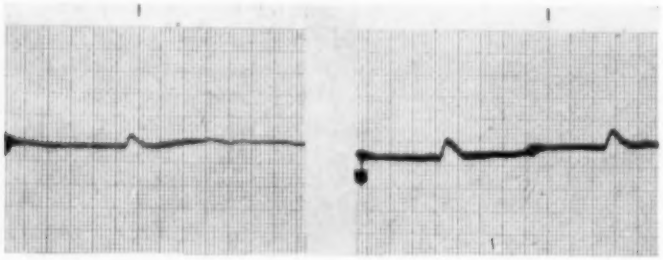


Fig. 6.—Left, N., 12 years old; xerosis 3+; b-potential 0.23 mv.; no night blindness. Right, A., 2½ years old; xerosis 1+; b-potential 0.35 mv.; vitamin A content 53 I. U. per 100 cc. of plasma.

*Electroretinograms and Vitamin A Levels in Normal Persons and in Xerosis With and Without Night Blindness*

| Clinical Condition | Electroretinography | | Vitamin A Estimation in Blood | |
|---|---|---|---|---|
| | No. of Eyes and Patients Studied | Average b-Potential, mv. | No. of Cases | Average Vitamin A, I. U. /100 Cc. of Plasma |
| Normal adults (cooperation +++ or more) | 19 eyes of 11 patients | 0.32 | 11 | 150 |
| Normal children | | | | |
| Above 7 yr. (cooperation +++ or more) | 11 eyes of 8 patients | 0.31 | 9 | 89 |
| Below 7 yr. (general anesthesia) | 6 eyes of 6 patients | 0.26 | 3 | 26 |
| Xerosis adults (cooperation +++ or more) | 16 eyes of 11 patients | 0.29 | 8 | 103 |
| Xerosis children | | | | |
| Above 7 yr | 9 eyes of 6 patients | 0.24 | 5 | 32 |
| Below 7 yr | 6 eyes of 6 patients | 0.18 | 3 | 20 |
| Xerosis with night blindness in adults | 19 eyes of 11 patients | All but 5 extinguished | 3 | 33 |
| Xerosis with night blindness in children | | | | |
| Above 7 yr | 11 eyes of 9 patients | All but 3 extinguished | 8 | 15 |
| Below 7 yr | 30 eyes of 23 patients | All but 3 extinguished | 6 | 15 |

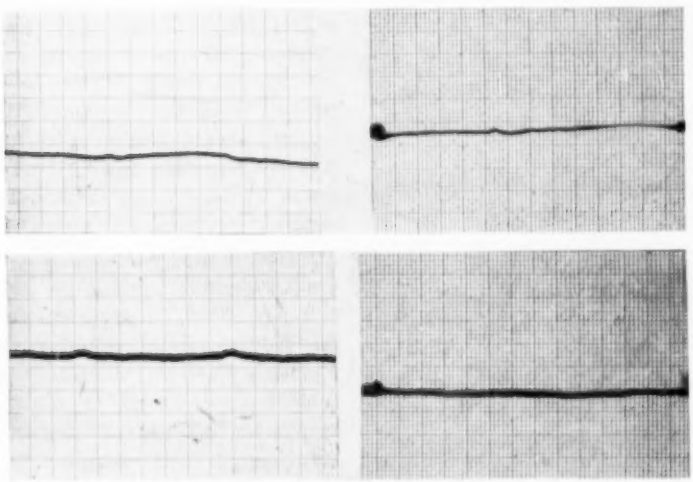


Fig. 7.—Above: Left: Mrs. R. R., aged 25 years; xerosis 4+, with night blindness; ERG nearly extinguished (media and fundi normal; vision 6/9 O. U.). Right: Mrs. K., aged 22 years; xerosis 1+, with night blindness for two months; b-potential 0.05 mv. (media and fundi normal).

Below: Left: B., aged 7 years; xerosis with night blindness for two months; b-potential 0.05 mv. Right, K., aged 5 years; xerosis 4+, with night blindness for 15 days; ERG completely extinguished; vitamin A 12 I. U. per 100 cc. of plasma.

In all 10 eyes of six children above the age of 7 years the electroretinogram was completely extinguished except for three, with b-potentials of 0.065, 0.058, and 0.10 mv.

Below the age of 7 years, of 30 eyes investigated, the electroretinogram was completely extinguished in all but 3, the b-potential of these 3 being also below 0.05 mv.

The average vitamin A content of 14 children was 15 I. U. per 100 cc., one child (D. B.), 10 years of age, with xerosis with night blindness, having presenting no vita-

min A content in the blood, as shown by chemical analysis.

The above averages are presented in the accompanying Table.

Figure 7 presents electroretinograms recorded in cases of xerosis with night blindness in various age groups.

### Comment

*Xerosis.*—It is apparent from the above observations that xerosis behaves differently in adults and in children. For example, xerosis in one case had existed for 15 years without causing any defect in night vision, and the patient came to the hospital for cosmetic reasons only. Again, in the case of Miss V. B., xerotic patches in both eyes had been known to exist for five years; yet she had b-potentials of 0.257 and 0.236 mv. in the two eyes. Again, in another case, age 41, the patient had a very large xerotic patch, which I have graded 3+, in each eye. The patient had observed them for over two years, and yet the b-potentials were 0.387 and 0.330 mv. In a fourth case (B. L.) with double bilateral xerotic patches for three to four years, the b-potentials were 0.39 and 0.4 mv., respectively.

Similarly, there were three cases of xerosis graded 2+ or more with vitamin A contents of 125, 130, and 185 I. U. per 100 cc. of plasma. It was also observed that xerosis existed in the conjunctiva of adults of upper economic status, where not only the food factor is satisfactory but the general condition is also above the average. Clinical malnutrition in adults with xerosis is not a common feature. Response to treatment is also very poor, e. g., xerosis had been known to exist for years, even though the patient had 60 massive injections of vitamin A over a period of nine months. The electroretinogram remained unaltered.

In the case of children, the observations were obviously different. Xerosis usually existed less than six months before the child attended the hospital. Again, in most of the children who come with xerosis clinical malnutrition is quite apparent, and the children usually belong to a poor class of society. In a good percentage of cases xerosis has followed a gastrointestinal upset. This xerosis either very soon disappears, with the improvement of the general condition, or, if untreated, soon leads to night blindness. Not only does the b-potential tend to be subnormal, but it was found completely extinguished in 5 out of the 27 cases, even though there was no night blindness. It may be that these cases were borderline, which if left untreated would very soon have developed night blindness.

Response to treatment is also rapid in children, large xerotic patches having disappeared with an average of six massive injections of vitamin A I. M., given every fourth day.

*Night Blindness.*—As stated above, children below the age of 15 years are particularly prone to develop night blindness as a result of vitamin A deficiency. This observation is borne out by the large number of outpatients brought to the Ophthalmic Hospital, Indore, with a history of night blindness. Most of them are usually ill-nourished and are of a poor economic status, and they respond to treatment with vitamin A.

Again, in general, either the electroretinogram was extinguished or the b-potential was extremely small. Treatment of these children resulted in rapid disappearance of night blindness, but the electroretinogram was comparatively slower in returning, while xerotic patches took still longer to disappear. As expected, the treatment in children was much more rapidly effective, both with regard to clinical symptoms and to the return of the normal electroretinogram.

Contrary to the observations in children, night blindness is not a common feature of vitamin A deficiency in adults, only 12 cases have been seen over a period of nearly two years out of thousands of outpatients at the Ophthalmic Hospital, Indore. In these cases night blindness was of an acquired nature, and other causes of night blindness had been definitely excluded.

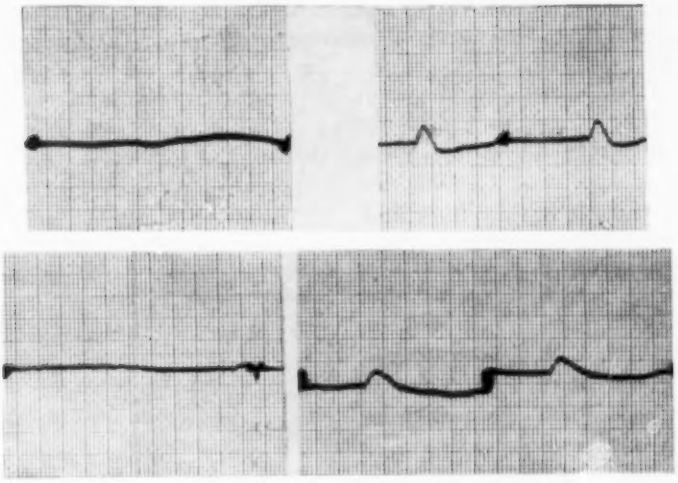


Fig. 8.—Above: R. K., aged 18; night blindness of nine days' duration. Left, ERG completely extinguished before treatment (Oct. 13, 1954); Vitamin A content 16 I. U. per 100 cc. of plasma. Right, ERG after five massive injections of vitamin A I. M. Night blindness nearly disappeared; b-potential now improved to 0.035 mv.; vitamin A content 20 I. U. per 100 cc. of plasma (Nov. 9, 1954).

Below: D. R., aged 6 years; xerosis 3+, with night blindness of one month's duration. Left, ERG before treatment completely extinguished (Nov. 9, 1954); vitamin A content 5 I. U. per 100 cc. of plasma. Right, ERG after seven massive injections of vitamin A. Night blindness practically disappeared; b-potential improved to 0.030 mv., and vitamin A content 21 I. U. per 100 cc. of plasma (Nov. 30, 1954).

Figure 8 presents the electroretinograms of the follow-up cases.

## GENERAL COMMENT

Some observations deserve a more detailed discussion.

A normal electroretinogram in xerosis in adults, so long as it is xerosis alone, is a very interesting finding. The interest is further heightened by a nearly, if not completely, normal vitamin A content of the blood. This raises the pertinent question whether primary xerosis, in the absence of any other cause in the conjunctiva, is a direct result of vitamin A deficiency or whether it is an indirect manifestation. This mystery is heightened by the poor response of xerotic patches to vitamin A administration in adults. Whatever relation exists between vitamin A content and xerosis is indicated only by the existence of xerosis in children, who if untreated very soon develop night blindness. The only conclusion that can be drawn from the observations and investigation of a very large number of cases with xerosis leads one to conclude that xerosis is not a direct manifestation of vitamin A deficiency, but is the result of some indirect or allied cause which has a close association with the vitamin A content of the blood. What that factor is cannot be deduced from these investigations, but it certainly opens up a field for further research.

An extinguished electroretinogram in cases of night blindness due to vitamin A deficiency has been demonstrated for the first time during these investigations. Professor Karpe * has only casually referred to the observation of an extinguished electroretinogram in a single experimental case of malnutrition. These investigations have conclusively proved that the onset of clinical manifestations of night blindness due to vitamin A deficiency is a deciding factor as to how the electroretinogram will be affected. The electroretinogram is suddenly extinguished as soon

* Karpe, G.: Personal communication to the author.

as the vitamin A content of blood falls to a level that causes clinical manifestation of night blindness.

These observations indicate that so long as a person has only xerosis, not only is the vitamin A content of the blood at a fairly normal level but his electroretinogram also remains unaffected; as soon as he develops night blindness, however, the electroretinogram is completely extinguished and the vitamin A of the blood falls to a minimum level.

Another observation that deserves discussion is the increased sensitivity of children to vitamin A deficiency. It is obvious from the foregoing observation that the vitamin A content of normal children below the age of 15 years is of a much lower order than that of adults. This may be due to a lower intake, more probably to a bigger demand during the developing stages of life. This also probably explains the greater frequency of night blindness in children due to vitamin A deficiency, whereas in adults, the demand being much less, the vitamin A content of the blood does not fall to a level low enough to cause night blindness.

Again, the finding of an extinguished electroretinogram in five cases of xerosis alone in children below the age of 7 years suggests that these children had reached a critical stage of vitamin A content and would very soon have developed night blindness if left untreated. The vitamin A content in one of these cases was only 17 I. U. per 100 cc. This, and the general finding of lower vitamin A content in children, accounts for the greater sensitiveness of children to vitamin A deficiency and explains why most of them very soon develop night blindness.

The minimum vitamin A level in the blood must, obviously, be extremely low because cases have been observed in which the vitamin A content had fallen to as low as 50 I. U./100 cc. of plasma and yet the electroretinogram remained normal and night blindness never developed. In cases of night blindness not only was the vitamin A content invariably low but the electroretinogram was also extinguished. The observations regarding the vitamin A estimation are made with reservations, and with full realization of the fact that chemical analysis of plasma for vitamin A gives variable results. The value attached to the chemical analysis during these investigations is a relative one, but is considered of value, because in all cases analysis was done under similar circumstances, in that blood collected was on a fasting stomach and was analyzed within three hours of its collection, and the chemical method adopted, as well as the photoelectrocolorimeter used, was the same during the whole period of the work.

Incidentally, these investigations throw an interesting light on the pathogenesis of night blindness and its association with the extinguished electroretinogram. The degeneration of the retina as a whole in retinitis pigmentosa, resulting in an extinguished electroretinogram, is not difficult to understand. A hypothesis put forward by Riggs, in his paper on electroretinography in cases of night blindness due to retinitis pigmentosa or in cases of congenital origin, suggests the existence of "holes in the retina" as the mode of an extinction of the electroretinogram in these cases. Obviously, observations set forth in this paper prove that this hypothesis is not necessarily correct. As is shown by this investigation, an electroretinogram can be completely extinguished even though the retina may be structurally normal, and only functionally affected, as in the case of vitamin A deficiency. That structural changes in the retina are necessary in order for an electroretinogram to be extinguished is also disproved by the observation that a retina which has lost its electric response completely may regain it fully with treatment with vitamin A. This leads to the conclusion that no organic change is necessary for the electroretinogram to be extinguished and proves that an electroretinogram represents the functioning capacity of the retina, rather than being related to its structural morphology.

## SUMMARY

1. An electroretinogram can be successfully recorded in most of the human subjects above the age of 7 years, while general anesthesia is usually necessary below that age.

2. The b-potential of a normal Indian adult is 0.32 mv., and that of a child between the ages of 7 and 15 years is 0.31 mv., and that below the age of 7 years, 0.26 mv.

3. The electroretinogram remains normal so long as the patient suffers from xerosis alone and the vitamin A content of the blood is above the minimum threshold level.

4. The electroretinogram is completely extinguished as soon as the vitamin A deficiency leads to the manifestation of night blindness and the vitamin A content falls below the minimum threshold level.

5. The absolute minimum vitamin A requirement in human beings must be of a very low order. The vitamin A threshold is in the neighborhood of 20 I. U./100 cc. of plasma in children below 15 years of age and a little higher in adults.

6. Children are much more susceptible to vitamin A deficiency than are adults and develop night blindness, as well as lose the electrical response in the retina, much more rapidly than adults.

7. Night blindness as a manifestation of vitamin A deficiency is much more frequent in children than in adults.

8. Children respond to treatment much more rapidly than adults.


## CONCLUSIONS

1. Xerosis is an indirect manifestation of vitamin A deficiency rather than a direct one.

2. Night blindness is a direct result of vitamin A deficiency.

3. A functional defect of the retina is enough to lead to an extinguished electric response, and a pathological and structural change is not a necessity.

4. An extinguished electroretinogram is a reversible phenomenon.

The Indian Council of Medical Research was responsible for the initiation of electroretinography in India. The Principal, Dr. B. C. Bose, and Prof. S. K. Mukerjee, Head of the Department of Medicine, Mahatma Gandhi Memorial Medical College, Indore, allowed me free access to the cardiograph.

Mahatma Gandhi Memorial Medical College.

## BIBLIOGRAPHY


de Andrade, L.: Importance of Direct Zonulotomy in Execution of Total Lens Extraction, Ophthalmologica **115**:78, 1948.

Dhanda, R. P.: Electroretinography in Vitamin A Deficiency, Technical Report of Scientific Advisory Board of the Indian Council of Medical Research, pp. 229 and 251, 1952-1953, and 219, 1954.

Marg, E.: Development of Electro-Oculography, A. M. A. Arch. Ophth. **45**:169, 1951.

Karpe, G.: Basis of Clinical Electro-Retinography, Acta ophth., Supp. 24, 1945.

# Cataracts Produced in Rats by 1,4-Dimethanesulfonoxybutane (Myleran)

CYRIL SOLOMON, M.D.
AMOS E. LIGHT, M.A.
and
E. J. DE BEER, Ph.D., Tuckahoe, N. Y.

Haddow and Timmis,[1] in the course of preparation of a series of sulfonic acid compounds, found only the sulfonic acid esters active in inhibiting the growth of certain tumors in animals. One ester in particular, 1,4-dimethanesulfonoxybutane, showed intense inhibition of the growth of Walker rat carcinoma No. 256 and a depressant action on circulating neutrophiles in rats. Clinical trials by Galton,[2] Galton and Till,[3] Wintrobe and associates,[4] and Petrakis and associates [5] have shown this drug to be of definite value in the treatment of chronic myeloid leukemia in humans.

During chronic toxicity tests on Myleran, cataracts were observed in the rats receiving relatively large amounts of the drug as compared with the therapeutic doses given humans. Certain aspects of these studies are described in the following report.

Received for publication Sept. 28, 1955.

Presented in part at the International Congress of Biochemistry, Brussels, Aug. 5, 1955.

Supplied as Myleran Brand 1,4-Dimethanesulfonoxybutane, Burroughs Wellcome & Company Inc., Tuckahoe, N. Y.

From the Wellcome Research Laboratories, Burroughs Wellcome & Company, Inc., Tuckahoe, N. Y., and the French Hospital, 330 W. 30th St., New York.



## EXPERIMENTAL PROCEDURE

Growing male albino rats (Carworth Farms), 45-60 gm. in weight, were fed ground Purina Fox Chow (with meat meal) diets containing various dose levels of Myleran. The animals were periodically examined for cataract formation, along with other physiological changes. Autopsies were performed, and tissue sections were obtained at appropriate times.

## RESULTS

Doses greater than 20 mg. of Myleran per kilogram of diet caused death before cataract formation. Doses less than 7.5 mg. per kilogram had no effect, even after 26 weeks. As shown in the accompanying Table, the doses between these limits did produce opacities in the rat's eyes, the time of appearance having an inverse relationship to the dose.

In other experiments it was found that cataracts once formed were irreversible, since re-alimentation on a drug-free control diet for periods up to eight weeks did not alleviate the condition. Likewise, various nutritional and chemical supplements, so far used, have had no inhibiting effect on the opacity forma-

*Cataract Formation in Relation to Dose of Myleran*
(10 Rats per Group)

| Dose of Myleran Mg./Kg. Diet | Average Survival, Days | Cataract Appearance in Rats | Drug Intake, Mg./Kg. 84-Day Wt./Day |
|---|---|---|---|
| 20 | 50 | 3 after 56 days (7 died) | 1.60 |
| 15 | >84 | 4 after 63 days | 0.89 |
| 10 | >84 | 4 after 70 days | 0.54 |
| 7.5 | >84 | 2 after 77 days | 0.35 |

tion. These studies are being reported in a separate communication.

Blood sugar determinations in rats receiving doses of 10 mg. of Myleran per kilogram of diet revealed that the values were significantly ($t$=5.5) elevated about 15% above the usual average level of 106.2 mg. per 100 cc. of blood found in the control animals. However, this increased level is not great enough to be the cause of cataract production as postulated by the criteria of Patterson.[6]

The earliest pathological changes appeared to be a marked increase in the mitosis of the lens epithelium, especially at the equatorial portion. This was followed by vacuolation in the subcapsular cortex, anteriorly, and perinuclear vacuolation. Finally, diffuse feathery opacities were found in the subcapsular cortex, anteriorly and posteriorly, as well as in the perinuclear region.

## COMMENT

Although the value of Myleran has been definitely established in the treatment of chronic myeloid leukemia, its mode of action is speculative. Bergel[7] considers it as a biological alkylating agent which reacts with certain cellular constituents in the cytoplasm or nucleus of cells. This alkylation in proteins may occur at the terminal undissociated $-NH_2$ groups and dissociated $-COOH$ groups and in the histidine moiety. The site of action in the nucleic acids may include the phosphate portion and the amino groups of the purines and pyrimidines.

In general, cataract may be considered as a loss of transparency in the lens of the eye due to altered physiochemical processes. The disturbance in the lens structure is either a swelling opacity, which is reversible, or a coagulation opacity, which is irreversible. Cataracts have been produced in animals by endocrine disturbances, thallium, ergot, naphthalene, galactose, dinitrophenol, deficiencies of vitamins and amino acids, and radiation.[8] 1,4-Dimethanesulfonoxybutane should now be added to this list, since this alphatic compound, in gamma quantities, has now been found to produce cataracts in rats. Galactose, on the other hand, is required to be at a 30% level in the diet for such action. It may be commented on here that even the lowest dose of Myleran per kilogram of body weight used to produce the rat cataracts is still about 10 times the dose used in the treatment of chronic myeloid leukemia in humans. Up to the present time no cataracts have been found in patients following the use of this drug. It also may be observed that the rats in the above experiments were young and growing animals. Studies are being continued in an attempt to follow the development of the cataracts. Nutritional and chemical adjuncts are being tested for activity in preventing the opacities. It is hoped that Myleran may prove to be useful in future studies of cataract formation.

The changes in the lens epithelium of the rat found following the administration of critical amounts of the drug are similar to those seen in cataracts produced by irradiation. However, the time needed at the dose levels described for the lens change is much shorter for the drug than for radiation. The latter usually requires many months to produce changes. Some similarity is not unexpected, since Myleran, like the nitrogen mustards, is included with the so-called "radiomimetics," which exhibit a number of comparable biological properties in common.* After intensive studies of growth curves and hematological responses in rats, Elson has concluded that Myleran has a specific radiomimetic effect on the myeloid tissues.[10] The changes in lens epithelium may prove to be useful in the evaluation of radiation-like effects of other chemotherapeutic drugs and radioisotopes.

## SUMMARY

The production of cataracts in rats by an aliphatic compound, 1,4-dimethanesulfonoxybutane (Myleran), is described.

The cataracts appear to be irreversible and, at the dose levels employed, could not be prevented by various nutritional and chemical adjuncts.

* References 7 and 9.

The pathology of the cataracts produced by Myleran in doses some 10 times those used therapeutically resembles that of the opacities caused by irradiation. This effect supports the theory of the radiomimetic activity of Myleran.

## REFERENCES


1. Haddow, A., and Timmis, G. M.: Myleran in Chronic Myeloid Leukæmia: Chemical Constitution and Biological Action, Lancet **1**:207, 1953.

2. Galton, D. A. G.: Myleran in Chronic Myeloid Leukæmia: Results of Treatment, Lancet **1**: 208, 1953.

3. Galton, D. A. G., and Till, M.: Myleran in Chronic Myeloid Leukemia, Lancet **1**:425, 1955.

4. Wintrobe, M. M.; Cartwright, G. E.; Fessas, P.; Haut, A., and Altman, S. J.: Chemotherapy of Leukemia, Hodgkin's Disease and Related Disorders, Ann. Int. Med. **41**:447, 1954.

5. Petrakis, M. L.; Bierman, H. R.; Kelly, K. H.; White, L. P., and Shimkin, M. B.: The Effect of 1,4-Dimethanesulfonoxybutane (GT-41 or Myleran) upon Leukemia, Cancer **7**:383, 1954.

6. Patterson, J. W.: Effect of Partial Starvation on Development of Diabetic Cataracts, Proc. Soc. Exper. Biol. & Med. **87**:395, 1954.

7. Bergel, F.: Attempts at Chemotherapy of Malignant Diseases, J. Pharm. & Pharmacol. **7**: 297, 1955.

8. Shlaifer, A.: Cataract and Its Etiology, Am. J. Optom. & Arch. Am. Acad. Optom. **31**:437, 1954.

9. Buschke, W.: Dystrophic Cataracts and Their Relation to Other "Metabolic" Cataracts, Arch. Ophth. **30**:751, 1943.

10. Elson, L. A.: A Comparison of the Effects of Radiation and Radiomimetic Chemicals on the Blood, Brit. J. Hæmatol. **1**:104, 1955.

# Corticosteroids in the Aqueous Humor of the Rabbit

**Paper Chromatography**

HARRY GREEN, Ph.D.
HENRY S. KROMAN, M.S.
and
IRVING H. LEOPOLD, M.D., Philadelphia

In a previous investigation[1] analysis of chloroform extracts of aqueous humor from normal rabbit eyes by the blue tetrazolium method indicated the presence of corticosteroids in quantities of the order of magnitude of 1-1.5γ per milliliter. Since the blue tetrazolium method neither permits the identification of individual compounds in a mixture nor is specific only for oxidizable corticoids, the extracted aqueous humor was fractionated by paper partition chromatography and analyzed for corticosteroids. The results of this investigation strongly indicate that at least part of the blue-tetrazolium-positive material present in aqueous humor is hydrocortisone.

## MATERIALS

The following purified crystalline corticosteroids were donated by Sharp & Dohme, Division of Merck & Company, Inc.: 11-dehydrocorticosterone (A); corticosterone (B); 11-desoxy-17-hydroxycorticosterone (S); cortisone (11-dehydro-17-hydroxycorticosterone, Compound E); hydrocortisone (17-hydroxycorticosterone, Compound F); hydrocortisone acetate; dihydrocortisone, and tetrahydrocortisone. Small aliquots of the samples were dissolved in absolute methanol in concentrations of 1γ and 3γ per microliter and stored at 8 C.

*Solvents.*—Toluene and propylene glycol, Eastman Kodak products, were used without additional treatment. Absolute methanol and chloroform, Mallinckrodt Chemical Works, were redistilled before use.

Filter paper, Whatman No. 1, cut into 17.5×42 cm. sheets, was fashioned into four parallel limbs 1×30 cm. per sheet, attached to a common head, as described by Burton and co-workers.[2]

Blue tetrazolium was purchased from the Nutritional Biochemicals Corp. and prepared as a 0.2% aqueous solution and mixed with 2 vol. of 10% NaOH prior to use.

*Chromatographic Apparatus.*—Cylindrical Pyrex jars, 24 in. high and 12 in. in diameter, with glass solvent troughs supported 18 in. from the bottom by a stainless steel stand, and Pyrex antisiphon rods were used. A starch-glycerin paste provided a tight seal between the jar and the plate glass cover.

*Spectrophotometry.*—A Beckman spectrophotometer Model DU was used to measure absorption spectra and optical densities of solutions contained in quartz or glass microcuvettes with 1 cm. light path and total volume of about 1 ml.

A Mineralight (Ultraviolet Products Corp., South Pasadena, Calif.) was used to examine the chromatogram under ultraviolet light.

## PROCEDURE

Adult pigmented rabbits, weighing 5-7 lb., were used. The aqueous humor was removed from the anterior chamber through a 26-gauge needle into a tuberculin syringe, as previously described.[1] In the absence of any grossly visible inflammation or synechia, the eyes were tapped four to six times at intervals of 72 hours. The aqueous humor was immediately mixed with chloroform and stored in the dark at 8 C until a sufficient pool had accumulated. The pooled samples were extracted four times with 5 vol. of chloroform. The pooled extract was concentrated to a volume of 0.5 ml. under the reduced pressure of a vacuum pump at a bath temperature of 45 C. The concentrated chloroform

Received for publication Sept. 6, 1955.

Department of Research, Wills Eye Hospital.

This investigation was supported in part by a research grant from the National Institute of Neurological Diseases and Blindness, of the National Institutes of Health, U. S. Public Health Service.

residue was applied in 5μl portions to the middle of the limb of the paper, 30 cm. from the bottom. A constant stream of warm air from a domestic hair dryer served to dry the applied spot, 1 cm. in diameter, during the application. The filter paper had been previously washed with 95% ethanol for 24 hours in a chromatographic jar by the descending technique, then air-dried, and impregnated by immersion in propylene glycol. The excess solvent was removed by pressing between two sheets of dry filter paper, as described by Pechet.[3]

Chromatography was performed by the descending technique of Burton and co-workers.[2] However, only 80 ml. of toluene saturated with propylene glycol was used in the solvent trough, instead of the larger volumes suggested by these authors. Large sheets of filter paper impregnated with the developing mixture lined the inside of the cylinder so as to achieve a constant saturated environment. The overflow of the developing solvent was collected in suitable Pyrex vessels and stored for future investigation.

## EXERIMENTAL STUDY

Paper chromatography was carried out at room temperature, and no attempt was made to maintain a constant temperature during the course of the development. In all cases samples of aqueous humor were compared with standard solutions of the crystalline corticosteroids run simultaneously in the same chromatographic cylinder under identical conditions. After completion of the chromatogram the paper was removed from the cylinder and dried in a gentle stream of warm air in the dark for from 8 to 10 hours.

The following procedures were used for the detection and quantitative estimation of the spots on the chromatogram: 1. Examination under ultraviolet light. 2. Treatment with blue tetrazolium-NaOH reagent, by spraying or dipping. 3. Elution of the spot, located by (1) and (2), above, on a parallel chromatogram, with 1.0 ml. of methanol for 20 minutes. The absorption spectrum of the methanol solution was determined at between 220 and 260 mμ. 4. Evaporation to dryness of the methanol solution used for ultraviolet spectrophotometry under reduced pressure by means of a vacuum pump. The residue was treated with 1.0 ml. of concentrated sulfuric acid and the absorption spectrum of the chromogen formed was determined at from 220 to 260 mμ. 4. Evaporation to dryness of the methanol solution used for ultraviolet spectrophotometry under reduced pressure by means of a vacuum pump. The residue was treated with 1.0 ml. of concentrated sulfuric acid and the absorption spectrum of the chromogen formed was determined at from 220 to 510 mμ, as previously described.[1] In each experiment controls of the reagents, as well as of the paper used for chromatography, were run simultaneously.

## RESULTS

Preliminary paper chromatography of the crystalline corticosteroids, followed by detection of the spots with the blue tetrazolium-NaOH reagent, indicated that only hydrocortisone possessed mobility characteristics similar to those of a spot derived from aqueous humor over a period of from 5 to 72 hours. Our attention was therefore directed to a comparison of the properties of the chromatogram of aqueous humor with those of hydrocortisone.

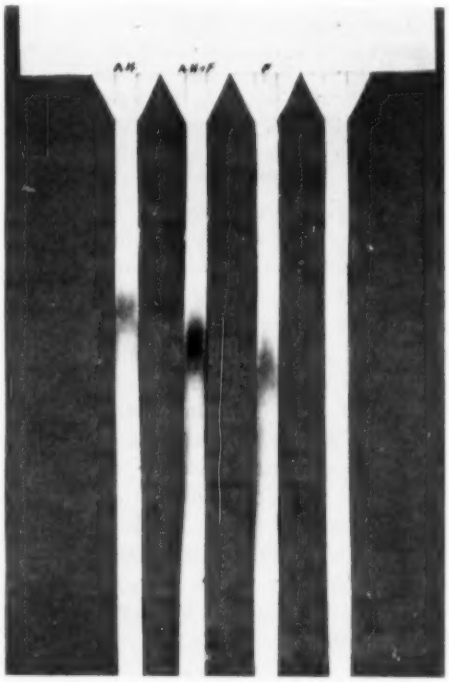


Fig. 1.—Forty-hour chromatogram of 3γ of hydrocortisone, the equivalent of 17 ml. of aqueous humor (chloroform extract), and a mixture of 3γ hydrocortisone and aqueous humor. Temperature during the development, 31-33 C.

*Mobility and Intensity of Zones.*—Figure 1 is a photograph of a typical 40-hour chromatogram of 3γ of hydrocortisone, the equivalent of 17 ml. of aqueous humor and a mixture of hydrocortisone and aqueous

humor, after having been dipped in the blue tetrazolium-NaOH reagent. It can be seen that the individual zones derived from hydrocortisone and aqueous humor have essentially the same mobility, and that the mixture of the two gave only a single zone, whose position on the chromatogram is the same as that from the two constituents.* In addition, the color intensities of the zones from the aqueous humor and hydrocortisone are

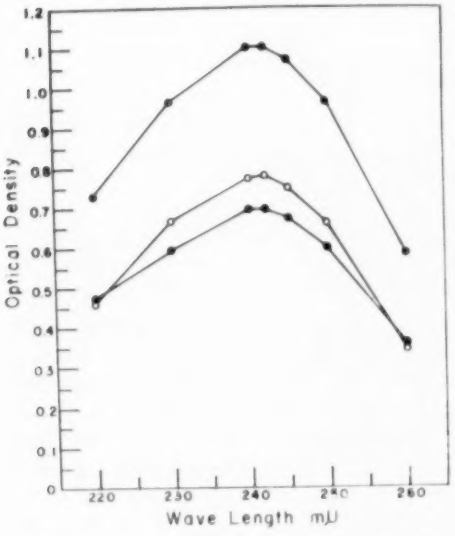



Fig. 2.—Ultraviolet absorption spectra. The individual zones were eluted from the chromatogram with 1.0 ml. of methanol. The line of clear circles represents 3γ of hydrocortisone; the line of solid circles, the equivalent of 17 ml. of aqueous humor (chloroform extract), and the line of half-solid circles, 3γ, a mixture of 3γ hydrocortisone.

roughly equal, while the zone derived from the mixture is more intense than that from either one. Similar results were obtained with chromatograms developed over 24 and 72 hours. In general, the mobilities of the three individual zones were approximately three-fourths and twice as fast, respectively, after 24 and 72 hours as those measured after 40 hours. The individual zones showed characteristic fluorescence when examined under ultraviolet light.

*Ultraviolet Absorption Spectrum.*—The zones on the chromatograms, located under ultraviolet light, were eluted with methanol and measured spectrophotometrically between 220 and 260 mμ. The results in the form of absorption curves are given in Figure 2 and clearly show in all three cases the presence of an absorption maximum at 242 mμ, corresponding to the $\Delta^4$-3 keto group. Since the optical density of hydrocortisone at 242 mμ can be shown to obey Beer's Law, at least for concentrations up to 10γ, it is apparent from the heights of the individual peaks that the zone derived from aqueous humor corresponds to about 3γ of hydrocortisone. In control experiments with hydrocortisone it was found that recovery after elution was approximately 80%, as measured by the optical density in the region of the maximum. It can also be seen that the optical density of the zone from the mixture is about 75% of that given by the sum of the individual optical densities.

*Sulfuric Acid Chromogen Absorption Spectrum.*—The absorption curves of the chromogens produced by the individual eluted zones after reaction with sulfuric acid are shown in Figure 3. It is obvious that all three curves are identical in shape with maxima at 240, 280, 390, and 475 mμ. Also, the close similarity in the heights of curves derived from hydrocortisone and aqueous humor again indicate that 17 ml. of pooled aqueous humor contains approximately 3γ of hydrocortisone. It is also apparent that the height of the curve given by the mixture is about equal to the sum of the heights of the individual curves.

*Overflow Solvent.*—The developing solvent that dripped off the paper during the

* The slight difference in mobilities between hydrocortisone (Compound F) and aqueous humor in Figure 1 may be due to the relatively elevated temperature (31-33 C), since between 23 and 29 C the mobilities are identical. The mobility of the mixed chromatogram did not vary more than 0.5 cm. from either of the individual chromatograms. Abelson and co-workers [4] have reported that with extracts of cerebrospinal fluid the addition of cortisone or hydrocortisone gave chromatograms whose mobilities were faster than those of the reference steroids alone.

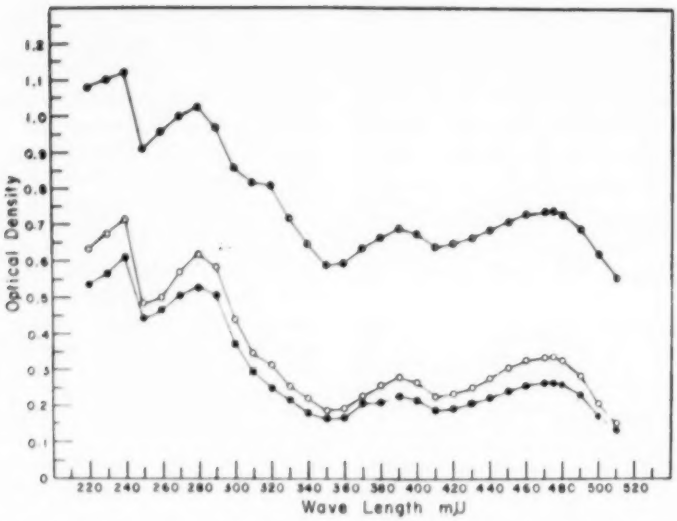



Fig. 3.—Absorption spectrum of the sulfuric acid chromagen. The methanol eluate was evaporated to dryness and the residue treated with sulfuric acid. The line of clear circles represents 3γ of hydrocortisone; the line of solid circles, the equivalent of 17 ml. of aqueous humor (chloroform extract), and the line of half-solid circles, a mixture of 3γ of hydrocortisone.

chromatography of the aqueous humor was collected and pooled. Chromatographic investigation of this material is in progress.

## COMMENT

Paper partition chromatography has been widely used as an analytical tool for the identification of a large variety of products. Although the information derived from paper chromatographic analysis alone may not be sufficient to identify any one substance, the systematic method developed by Zaffaroni and co-workers, embracing both paper chromatography and spectrophotometry in sulfuric acid, permits identification of corticosteroids with confidence. The combined application of the two techniques, moreover, affords a simple method of determining homogeneity of a sample.

The identification of hydrocortisone, Compound F, as a constituent of the primary aqueous humor of the normal rabbit eye is based upon the following analytical criteria: (1) The chromatographic behavior of aqueous humor over a period of 72 hours is almost identical with that of a pure, crystalline sample of hydrocortisone, and a mixed chromatogram of the two materials gave only one zone whose movement was the same as that of both constituents; (2) ultraviolet light examination and reaction to blue tetrazolium were the same for all three individual zones; (3) the absorption curves of the eluted zone derived from aqueous humor before and after reaction with sulfuric acid were identical with the corresponding curves given by the chromatograms of hydrocortisone and a mixture of hydrocortisone and aqueous humor. From a comparison of the intensity of the purple diformazans produced by reaction of the chromatograms with blue tetrazolium-NaOH reagent, it is estimated that 3γ of hydrocortisone is present in 17 ml. of primary aqueous humor of the rabbit eye (0.17γ/ml.).

Recently Bush [5] has reported that hydrocortisone and corticosterone are the predominant corticosteroid components present in the adrenal venous blood of the rabbit and that the ratio is 20:1 in favor of the latter. Since corticosterone has a faster mobility than does hydrocortisone, moving off the paper after 17 hours, the chromatograms were developed for only 5 hours. For this time period

crystalline hydrocortisone descended a distance of about 2 cm. from the origin and corticosterone a distance of about 6 cm. The chromatogram from aqueous humor, however, corresponded only to the position of hydrocortisone; no spot corresponding to that of corticosterone could be detected. Since the blue tetrazolium spray method is capable of detecting as little as 1γ of α-ketosteroids on paper chromatograms, it is reasonable to conclude that even if aqueous humor contains corticosterone in quantities less than 1γ/17 ml., the ratio of the concentration (B : F) would be much less than 1.0. The possibility that the acetate of corticosterone, rather than the free alcohol, may be present in the aqueous humor has not been evaluated, since a sample of corticosterone acetate was not available for comparison. In the absence of specific information with regard to the running properties of the acetate, which, it is known, is much faster than the free alcohol, the possible presence of the acetate in the overflow cannot be excluded. This phase of the problem is now being investigated. This consideration, however, does not apply to hydrocortisone acetate, since the latter, if present in the aqueous humor, in concentrations of 1γ/17 ml. or more, would have been detected in a 24-hour chromatogram.

SUMMARY

Concentrated chloroform extracts of 17 ml. of aqueous humor from rabbit eyes were fractionated by the paper chromatographic technique of Zaffaroni and co-workers, using the toluene-propylene glycol system, and analyzed for corticosteroids.

The following crystalline corticosteroids were used as primary standards for comparison: 11-dehydrocorticosterone (A); corticosterone (B); 11-desoxy-17-hydroxycorticosterone (S); cortisone (11-dehydro-17-hydroxycorticosterone, Compound E); hydrocortisone ((17-hydroxycorticosterone, Compound F); hydrocortisone acetate; dihydrocortisone, and tetrahydrocortisone.

Aqueous humor gave one single zone on the chromatogram after 5 to 72 hours, the running properties of which were identical with those of crystalline hydrocortisone. The zones were examined by ultraviolet light and by reaction with blue tetrazolium-NaOH reagent.

Elution of the chromatographic zone with methanol gave a solution whose ultraviolet spectrum showed a maximum of 242 mμ, characteristic of the $\Delta^4$-3 keto group.

The sulfuric acid chromagen spectrum of the eluted spot was practically identical in form and shape with that given by hydrocortisone.

From a comparison of the intensity of the blue tetrazolium spots and the heights of the absorption maxima, it is estimated that about 3γ of hydrocortisone is present in 17 ml. of aqueous humor of rabbit eyes.

The overflow solvent of the chromatography from 24 to 72 hours is being analyzed.

REFERENCES

1. Green, H.; Sawyer, J. L., and Leopold, I. H.: Investigation of Corticosteroids in the Aqueous Humor of Normal Animal Eyes: II. Further Observations, Am. J. Ophth. **36**:871, 1955.

2. Burton, R. B.; Zaffaroni, A., and Keutmann, E. H.: Paper Chromatography of Steroids: II. Corticosteroids and Related Compounds, J. Biol. Chem. **188**:763, 1951.

3. Pechet, M. M.: Methods for the Chromatographic Separation of Very Polar Steroids, Science **121**:39, 1955.

4. Abelson, D.; Baron, D. N., and Toakley, J. G.: Studies of Cerebrospinal Fluid Following Oral Administration of Cortisone Acetate or Hydrocortisone, J. Endocrinol. **12**:87, 1955.

5. Bush, I. E.: Species Differences and Other Factors Influencing Adrenocortical Secretion, in Ciba Foundation Colloquia on Endocrinology, London, J. & A. Churchill, Ltd., 1953, Vol. 7, p. 210.

# Keratitis and Scleritis Associated with Felty's Syndrome

PAUL J. OSTRIKER, M.D.
MARILYN OSTRIKER, M.D.
and
MORTIMER A. LASKY, M.D., Brooklyn

This paper is a report of a case with serious ocular complications associated with Felty's syndrome, a syndrome whose cardinal triad of features consists of chronic rheumatoid arthritis, splenomegaly, and leucopenia. A search of the literature fails to reveal any previous report of ocular findings with Felty's syndrome, except for one brief reference. This reference [1] concerned a case of Felty's syndrome in which an eye was enucleated for endophthalmitis and in which, unfortunately, there was no pathologic study of the enucleated eye. We believe our case is unique in that a splenectomy was performed in the hope of saving an eye.

## REPORT OF A CASE

*History.*—The patient, a 58-year-old white woman, with known rheumatoid arthritis for 16 years, had been treated privately for several years for recurrent keratitis of undisclosed nature. She was admitted to the eye service of another hospital in August, 1953, with chief complaints of pain in the left eye and lid swelling. On admission the left globe showed 4+ superficial and deep injection, with marked chemosis and lid swelling, soft tension, hazy cornea, heavy aqueous flare, gross exudate in the anterior chamber, and posterior synechiae. Three days later a lesion of the sclera was noted superonasally near the equator. There was a slough of the sclera and of the overlying conjunctiva, with the blue color of the underlying choroid showing through. The eye responded well to treatment with mydriatics and local and systemic cortisone, and in about two weeks the scleral crater was completely filled and the sclera glistening white. The cornea cleared, and the iridocyclitis subsided. She was discharged and had no further ocular complaints until seven months later.

In May, 1954, she was admitted to the Ophthalmological Service of the Jewish Hospital of Brooklyn with redness, pain, and loss of vision in the left eye for one week. On general examination the patient appeared emaciated, pale, and chronically ill. She had a markedly enlarged spleen, with widespread typical rheumatoid arthritic involvement of her joints. The peripheral blood count and differential cell count showed a marked leucopenia (WBC's ranged from 1,300/cu. mm. to 2000/cu. mm.) with relative lymphocytosis, increased platelets, and a moderate microcytic hypochromic anemia (RBC 2,600,000/cu. mm.). The sternal bone marrow puncture showed a cell-rich marrow with a slight increase of plasma cells, a marked left shift of WBC's, with band forms predominating, markedly increased megakaryocytes, and a moderate erythroblastosis. Splenic puncture showed normal splenic lymphocytes, and no abnormalities were noted. A special peripheral blood preparation for lupus erythematosus cells was negative. Other studies, including liver function tests, were done and were essentially noncontributory. After ruling out disseminated lupus erythematosus, Hodgkin's disease, and leukemia in the differential diagnosis, medical and hematological consultants concurred in the diagnosis of Felty's syndrome.

Ocular examination showed the following: The right eye was normal in all respects. In the left eye, visual acuity was light perception only; the globe showed 3+ diffuse injection, with ciliary flush, and the cornea was markedly and diffusely hazy around a paracentral ulcer about 3 mm. in diameter. The tension could not be determined because of exquisite tenderness of the globe.

Despite treatment with local atropine, oxytetracycline (Terramycin), and cortisone solutions, and later I. V. corticotropin, the ulcer progressively worsened and perforated five days after admission, with iris prolapsed through the site of perforation.

Received for publication Sept. 20, 1955.

From the Ophthalmological Service, Jewish Hospital of Brooklyn.

Enucleation was performed, and the pathologic report was as follows*:

*Microscopic Study.*—Meridional sections of the entire bulb show a small, partially collapsed, and distorted globe. The striking abnormality is the presence of a defect in the central portion of the cornea. This is filled with purulent exudate and partially resurfaced by a regenerative growth of corneal epithelium. The corneal stroma bordering on the defect is heavily infiltrated with polymorphonuclear leucocytes. There are some fragments of Bowman's membrane, but for the most part this layer is absent. The epithelium over the margins of the defect has been elevated by some hemorrhage and by some inflammatory exudation, so that it presents a blood-like elevation at various points. There has evidently been a long-standing vascular pannus encroaching on the margins of the cornea. The episcleral tissue in the ciliary region is excessively vascular. It contains infiltrating leucocytes, which are a mixture of granulocytes and lymphocytes. No granulomatous tissue is seen in this region, and, although a chronic episcleritis is present, it does not suggest the type of lesion seen in rheumatoid disease.

The iris has prolapsed into the corneal defect. It is entirely covered anteriorly by exudate, while the iris tissue itself is heavily infiltrated by acute inflammatory cells. Some exudate also lies in the narrow remnants of the anterior chamber, just in front of the prolapsed iris. Inflammatory infiltration in the ciliary body is relatively mild, and toward the posterior limits of the flat portion of the ciliary body there are only focal lymphocytic aggregations. There has been exudation from the ciliary body in the region of the ora serrata with some proliferation of pigmented and nonpigmented ciliary epithelium and some new formation of scar tissue, evidently the result of organization of ciliary exudate. The periphery of the retina has been somewhat dislocated and disorganized as the result of traction of this membrane. The membrane, however, does not extend forward into the pupillary or postlenticular region. There is no sign of the lens. It has evidently been completely extruded with its capsule. Very little inflammation is seen in the posterior segment. The retina has been slightly detached, and there is albuminous fluid adherent to its inner surface. Focally there is very early growth of capillaries into this coagulated fluid (beginning retinitis proliferans interna).

Typical arthritic deformities of the hands.

* Dr. J. Arnold deVeer, Pathologist, Brooklyn Eye and Ear Hospital, made the pathologic study and report.

An occasional retinal blood vessel shows local leucocytosis with margination. Otherwise there is very little retinal inflammation.

The choroid is practically free of inflammation, and the sclera, although relaxed and distorted, is not otherwise abnormal. The optic nerve entrance and the nerve are not seen in the sections submitted.

*Diagnosis.* — Chronic episcleritis, nonspecific; corneal ulcer with perforation; acute iridocyclitis; prolapse of iris; aphakia, and retinal detachment, slight.

The postoperative course following the enucleation of the left eye was uneventful, and the patient was discharged to the OPD. Two weeks later she complained of blurring and burning in the right eye. Examination revealed slight perilimbal injection and diffuse punctate superficial staining of the cornea with fluorescein. The corneal stroma, anterior chamber, and iris appeared uninvolved. Corneal sensation was decreased. She was immediately readmitted to the hospital for work-up and evaluation, as it was feared that the same process which destroyed the left eye was developing in her right eye. It was felt that her low white blood cell count lowered her resistance to infection and that medical means of elevating her white blood cell count should be considered. (It is interesting that soon after appearance of the above eye symptoms she developed a paronychia of her thumb, which was difficult to control.) During the next few days, despite intensive local and systemic antibiotic therapy, the superficial punctate keratitis became severer. The Schirmer test for tearing and the blood vitamin A levels were within normal limits. Cortisone was not used because of the previous adverse effect on the left eye. The best corrected acuity in the right eye was 20/200. Hematological and medical consultants advised splenectomy, which was performed on June 24, 1954. We felt that the ophthalmological indication for the splenectomy was to protect the devitalized cornea against infection and ultimate perforation by the expected correction of the leucopenia. Also, we believed that improving the general condition of the patient and the possible improvement of other unknown factors that result from the splenectomy in these cases could only have a beneficial effect on the eye.

Her WBC's, which had been running about 2000/cu. mm. prior to splenectomy, rose to 20,000/cu. mm. immediately after splenectomy, fell somewhat thereafter, and have remained between 6,000 and 10,000/cu. mm. up to the present date. In addition, following splenectomy, the right eye has been far less irritable, and, although there still is occasional superficial punctate staining of the cornea, this is not nearly as severe as formerly. The cornea no longer appeared hazy as it did preoperatively, but had normal luster. Her best corrected vision improved from 20/200, preoperatively, to 20/50, at which it has remained up to the date of this report.

COMMENT

In 1924 Felty [2] described the syndrome of which the cardinal features were chronic rheumatoid arthritis, splenomegaly, and leucopenia. Subsequently, other authors described similar cases, and the term Felty's syndrome gained widespread usage. Other features, more rarely present in the reported cases, were malnutrition, yellow-brown pigmentation of the exposed skin surfaces, secondary anemia, lymphadenopathy, low-grade fever, hepatomegaly, and predominance in the middle-aged group. Current medical opinion, however, appears divided concerning the value or accuracy of considering Felty's syndrome as a specific clinicopathologic entity. One group considers Felty's syndrome to be merely an atypical form of ordinary rheumatoid arthritis, the splenomegaly and leucopenia possibly having an unrelated etiology.† This group feels that the term Felty's syndrome should be discontinued.[4] Another group,‡ however, believes there is value in retaining the term for classification purposes. Dameshek believes Felty's syndrome to be a form of splenic leucopenia due to involvement of the spleen in the chronic infectious or toxic process of rheumatoid arthritis. He believes the hypersplenism produces leucopenia by the enlarged spleen elaborating a hormone that inhibits the bone marrow in the maturation or liberation of leucocytes. Others explain that the hypersplenism produces leucopenia by a sequestration or phagocytosis of the leucocytes by the enlarged hyperactive spleen. Whatever the mechanism, most of the authorities agree on a hypersplenism factor producing the leucopenia in Felty's syndrome and agree on the advisability of splenectomy in many of these cases. There are several reports § of improvement or correction of the leucopenia in Felty's syndrome by splenec-

† References 1, 3, and 4.

‡ References 5 and 6.

§ References 7 to 12.

tomy, the rationale being a direct attack against the proposed hypersplenism mechanism.

Felty's syndrome is often regarded as a condition in the adult analogous to Still's disease in children. However, an important difference is that there is a leucopenia in Felty's syndrome, whereas the leucocyte count in Still's disease is usually normal, or, if altered, is elevated. In the European literature an almost identical syndrome with Felty's syndrome has been described and is referred to as the Still-Chauffard syndrome.

In discussing this case, it might be advisable to review briefly the ocular findings described usually as being associated with rheumatoid arthritis per se and to consider how they may apply to this case. Ocular manifestations frequently described for rheumatoid arthritis are iridocyclitis, scleromalacia perforans, Sjögren's syndrome, and iridocyclitis with band keratitis in Still's disease.[13]

We do not believe that the purulent iridocyclitis in this case is the typical endogenous, nongranulomatous iridocyclitis usually described with rheumatoid arthritis. In our case it was probably secondary to the corneal ulceration. Although superficial punctate keratitis was present, except for the arthritis, there were no other ocular or general findings suggesting a Sjögren syndrome, and the Schirmer test was negative. Clinically the scleral lesion resembled, and undoubtedly was, scleromalacia perforans of the excavating type. There were no scleral nodules, and the histopathologic report of the healed scleral lesion does not show the typical features of a rheumatoid granuloma, i. e., fibrinoid degeneration and necrosis of collagen, as found by Anderson and Margolis.[14]

## SUMMARY AND CONCLUSIONS

A case report and discussion of a scleritis and keratitis associated with Felty's syndrome are presented. It is believed that this report is the first in the literature that shows this association.

Felty's syndrome consists essentially of chronic rheumatoid arthritis, splenomegaly, and leucopenia. In the reported case the left eye developed scleromalacia perforans and later an uncontrollable central ulcer of the cornea, which perforated and went on to enucleation. Later, the right eye became irritable and developed a superficial punctate keratitis, which progressively worsened despite conventional therapy. It was felt that the leucopenia associated with the Felty syndrome lowered the patient's resistance to infection, and splenectomy was performed. (Whole blood transfusions, which had previously been administered, had produced only a very transient beneficial effect.) Following the splenectomy, the white blood cell count promptly rose to above normal, the keratitis in her right eye was ameliorated, and the best corrected visual acuity improved from 20/200 to 20/50, as of the date of this report. Histopathologic study of the enucleated left eye did not show any specific rheumatoid features.

We believe the ocular involvement in this case was severer than might be expected with the ordinary rheumatoid arthritis because of the associated leucopenia. We also believe that in the future it might be advisable to examine the eyes periodically in cases of Felty's syndrome and to keep splenectomy in mind where a scleritis and/or keratitis appears uncontrollable and threatens destruction of the eye.

284 New York Ave. (6).

## REFERENCES

1. Talkov, R. H.; Bauer, W., and Short, C. L.: Rheumatoid Arthritis Associated Splenomegaly and Leukopenia, New England J. Med. **227**:395-399 (Sept. 10) 1942.

2. Felty, A. R.: Chronic Arthritis in the Adult Associated with Splenomegaly and Leukopenia, Bull. Johns Hopkins Hosp. **35**:16-20 (Jan.) 1924.

3. Cecil, R. L.: A Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1948, p. 1436.

4. Curtis, A. C., and Pollard, H. M.: Felty's Syndrome: Its Several Features, Including Tissue Changes, Compared with Other Forms of Rheumatoid Arthritis, Ann. Int. Med. **13**:2265-2284 (June) 1940.

5. Lockie, L. M.; Sanes, S., and Vaughan, S. L.: Chronic Arthritis Associated with Neutrophilic Leukopenia, Splenomegaly and Hepatomegaly: "Felty's Syndrome," Am. J. Clin. Path. **12**:372-379 (July) 1942.

6. Dameshek, W.: Leukopenia and Agranulocytosis, in Oxford Loose-Leaf Medicine, edited by H. A. Christian, New York, Oxford University Press, 1944, Vol. 2, Pt. 3, pp. 841-848.

7. Craven, E. B., Jr.: Splenectomy in Chronic Arthritis Associated with Splenomegaly and Leukopenia (Felty's Syndrome), J. A. M. A. **102**:823-826 (March 17) 1932.

8. Hanrahan, E. M., Jr., and Miller, S. R.: Effect of Splenectomy in Felty's Syndrome, J. A. M. A. **99**:1247-1249 (Oct. 8) 1932.

9. Hirschboeck, J. S.: Hematologic Effects of Splenectomy in Still-Chauffard-Felty Syndrome: Report of 2 Cases, Blood **1**:247-255 (May) 1946.

10. Smith, S., and McCabe, E. S.: Primary Splenic Neutropenia with Arthritis (So-Called Felty Syndrome): Its Treatment by Splenectomy, Ann. Int. Med. **29**:445-455 (Sept.) 1948.

11. Kanar, E. A., and others: Felty Syndrome: Report of 2 Cases Treated by Splenectomy, West. J. Surg. **58**:670-681 (Dec.) 1950.

12. Hutt, M. S. R.; Richardson, J. S., and Staffurth, J. S.: Felty Syndrome: Report of 4 Cases Treated by Splenectomy, Quart. J. Med. **20**:57-73 (Jan.) 1951.

13. Sorsby, A.: Systemic Ophthalmology, London, Butterworth & Co., Ltd., 1951.

14. Anderson, B., and Margolis, G.: Scleromalacia, Am. J. Ophth. **35**:917-930 (July) 1952.

# Biologic Effects Studies on Microwave Radiation

## Time and Power Thresholds for Production of Lens Opacities by 12.3 Cm. Microwaves

D. B. WILLIAMS, B.S., Randolph Field, Texas
J. P. MONAHAN, M.D., London, England
W. J. NICHOLSON, B.S.
Kirtland Air Force Base, N. Mex.
and
J. J. ALDRICH, M.S., Randolph Field, Texas

Although cataract production has not been established as a microwave effect in humans,* the formation of lens opacities in animals subjected to 12.3 cm. radiation † suggests the need for precautions in the administration of ocular diathermy or in situations where exposure of the eye is required for the operation of microwave generators.‡ Unfortunately, the lack of basic information as to the radiation dose and dose rates employed in previous studies has thus far precluded the development of standards which define ocular tolerance to microwaves. As an initial effort in this direction, the present investigation is designed to establish the time and power requirements for experimental opacity production by single doses of 12.3 cm. radiation. Both the wave length and the power levels employed for this purpose are of interest in the applied fields of microwave diathermy, radar communications, and microwave research.

The chief source of information on lens damage by microwaves stems from the animal studies of Daily and associates § and Richardson and associates.[9] In these investigations opacity formation was found to be an extreme effect caused by high-power levels of exposure to 12.3 cm. radiation from Director C of the Raytheon Microtherm. It is notable that both research groups demonstrated opacities resulting from repeated exposures without having first established the minimum single dose of radiation which causes lens damage at a given level.

The former group of workers produced lens opacities in dogs and rabbits by repeated exposure to power levels initially established by operation of the microwave generator at 94 and 122 watts of power output. Field intensity was otherwise varied by selection of exposure positions at a distance of 1.5 to 5.0 in. from the antenna. The latter research group produced opacities by irradiating the eyes of rabbits at a constant distance of 2 in. from a 100-watt source. Single exposures of 15 to 20 minutes' duration produced lesions within three to nine days after irradiation. Repeated exposures, each of 10 to 12 minutes in duration, were effective within 15 days, except for one instance, of 42 days after the last exposure period. Vitreous temperatures of 51 to 55 C at the posterior pole of the lens were characteristic of opacity production by single exposures.

Received for publication July 25, 1955.

Department of Radiobiology, U. S. A. F. School of Aviation Medicine (Mr. Williams and Mr. Aldrich), St. John's Hospital, Lisle St., Leicester Sq., W. C. 2, (Dr. Monahan). Biophysics Division, AF Special Weapons Center (Mr. Nicholson).

This work was accomplished at the Radiobiology Laboratory, Atomic Warfare Directorate, Air Force Cambridge Research Center, Air Research and Development Command, Cambridge, Mass.

* References 1 and 2.

† References 3 to 5.

‡ References 5 to 9.

§ References 3 and 4.

Although the foregoing investigations are notably lacking in information as to the actual power density responsible for opacity formation, an estimate in these terms is found in a technical report of Salisbury and associates.[9] These authors cautioned that exposure to 3 watts/sq. cm. was dangerous with respect to lens damage. A single 10-minute exposure to 12.3 cm. radiation at this estimated power level produced opacities in the eyes of rabbits within 9 to 10 days after irradiation.

According to Herrick and Krusen,[6] a primary obstacle to the formulation of ocular tolerance standards has been the inherent difficulty in measuring field strength of microwave energy in free space. With the development of power measurement instrumentation and technique for this purpose,‖ it was possible in the present study to relate opacity production to the power density prevailing at the position of exposure.

Fifty-eight anesthetized rabbits were used to establish the minimum exposure time and power requirements for opacities produced by a single dose of radiation up to 90 minutes in duration. In order to establish the trend of threshold requirements beyond 90 minutes, four additional animals, two animals at each power level, were irradiated for 4.5 hours at 0.12 and 0.22 watt/sq. cm. Seventeen animals were used to determine the ocular and whole-body temperature characteristics of threshold exposures.

## MATERIALS AND METHODS

*Animals and Anesthesia.*—Male New Zealand white rabbits of the same generic strain and about 10 to 15 weeks of age were used in this investigation. Sodium pentobarbital (approximately 35 mg. per kilogram of body weight) injected into the marginal vein of the ear produced anesthesia for short periods of time (one-half hour). The method allowed for additional injections for longer periods of exposure.

*Radiation Source.*—The Raytheon Microtherm, Model CDM4, was employed as a source of high-frequency radiation. This instrument is rated at approximately 100 watts of power output at 100% power-meter setting. The power output is continuous wave radiation at 2450 mc/sec., producing a wave length of 12.3 cm. The calibration of the Microtherm [10] is described in the Appendix to this report.

*Ocular Exposures.*—The left eye served as a control for the right eye, which was exposed at 2 in. from Director C of the Microtherm. Distance was measured by use of a cylindrical wooden spacer, 2 in. long and ¼ in. in diameter, inserted between the cornea of the eye and the plastic housing in front of the dipole cross-over of the deflector. Duration of irradiation and power levels were varied between the limits of 3.5 and 8 minutes at 100% output (0.59 watt/sq. cm.) and 90 minutes at 35% output (0.24 watt/sq. cm.). After a single exposure was made to the open eye, each animal was periodically observed for 90 days, and in some cases for 6 months. Examination of both eyes before and after irradiation was made with the May ophthalmoscope. The results of this exposure series are presented in Table 1 and are resolved into a threshold for opacity formation in Figure 1. None of the control eyes developed opacities during the period of observation.

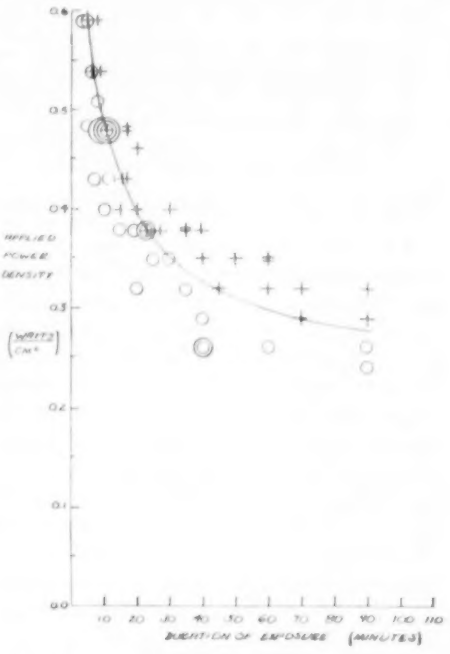



Fig. 1.—Exposure-time and power-density requirements for experimental opacity production by 12.3 cm. microwaves.

‖ Pankiewcz, C. L.: Rome Air Development Center, Griffis Air Force Base, New York; personal communication to the authors.

TABLE 1.—*Experimental Opacities Produced by Exposing the Open Eyes of Anesthetized Rabbits to 12.3 Cm. Microwaves*

| Animal No. | Generator, Per Cent of Total Power Output | Applied Power Density,* Watt/Sq. Cm. | Duration of Exposure, Min. | Opacity of Lens | Days After Exposure Until Appearance of Opacity |
|---|---|---|---|---|---|
| 1 | 100 | 0.59 | 8 | Minimal | 5 |
| 2 | 100 | 0.59 | 5 | Minimal | 12† |
| 3 | 100 | 0.59 | 5 | None | .. |
| 4 | 100 | 0.59 | 3.5 | None | .. |
| 5 | 90 | 0.54 | 9 | Diffuse | 1-3 |
| 6 | 90 | 0.54 | 7 | Minimal | 11 |
| 7 | 90 | 0.54 | 6 | None | .. |
| 8 | 85 | 0.51 | 8 | None | .. |
| 9 | 80 | 0.48 | 17 | Diffuse | 2 |
| 10 | 80 | 0.48 | 17 | Diffuse | 1 |
| 11 | 80 | 0.48 | 15 | Circumscribed | 7 |
| 12 | 80 | 0.48 | 15 | Diffuse | 1 |
| 13 | 80 | 0.48 | 13 | Circumscribed | 8 |
| 14 | 80 | 0.48 | 11 | Diffuse | 5 |
| 15 | 80 | 0.48 | 11 | None | .. |
| 16 | 80 | 0.48 | 11 | None | .. |
| 17 | 80 | 0.48 | 9 | None | .. |
| 18 | 80 | 0.48 | 10 | None | .. |
| 19 | 80 | 0.48 | 5 | None | .. |
| 20 | 75 | 0.46 | 20 | Diffuse | 1-3 |
| 21 | 70 | 0.43 | 17 | Minimal | 5-8 |
| 22 | 70 | 0.43 | 16 | Minimal | 3-10 |
| 23 | 70 | 0.43 | 12 | None | .. |
| 24 | 70 | 0.43 | 7 | None | .. |
| 25 | 65 | 0.40 | 30 | Circumscribed | 10 |
| 26 | 65 | 0.40 | 20 | Diffuse | 1 |
| 27 | 65 | 0.40 | 15 | Minimal | 11-14 |
| 28 | 65 | 0.40 | 10 | None | .. |
| 29 | 60 | 0.38 | 40 | Circumscribed | 4-7 |
| 30 | 60 | 0.38 | 35 | Minimal | 12-14† |
| 31 | 60 | 0.38 | 35 | Minimal | 7-13 |
| 32 | 60 | 0.38 | 27 | Circumscribed | 4 |
| 33 | 60 | 0.38 | 25 | Minimal | 2-6† |
| 34 | 60 | 0.38 | 23 | Diffuse | 3 |
| 35 | 60 | 0.38 | 23 | None | .. |
| 36 | 60 | 0.38 | 23 | None | .. |
| 37 | 60 | 0.38 | 20 | None | .. |
| 38 | 60 | 0.38 | 15 | None | .. |
| 39 | 55 | 0.35 | 60 | Diffuse | 2 |
| 40 | 55 | 0.35 | 60 | Diffuse | 2-6 |
| 41 | 55 | 0.35 | 50 | Minimal | 12 |
| 42 | 55 | 0.35 | 40 | Circumscribed | 3-6 |
| 43 | 55 | 0.35 | 30 | None | .. |
| 44 | 55 | 0.35 | 25 | None | .. |
| 45 | 50 | 0.32 | 90 | Circumscribed | 3-5 |
| 46 | 50 | 0.32 | 70 | Diffuse | 1 |
| 47 | 50 | 0.32 | 60 | Diffuse | 2-3 |
| 48 | 50 | 0.32 | 45 | Minimal | 11-12 |
| 49 | 50 | 0.32 | 35 | None | .. |
| 50 | 50 | 0.32 | 20 | None | .. |
| 51 | 45 | 0.29 | 90 | Diffuse | 1-4 |
| 52 | 45 | 0.29 | 70 | Diffuse | 3-4 |
| 53 | 45 | 0.29 | 40 | None | .. |
| 54 | 40 | 0.26 | 90 | None | .. |
| 55 | 40 | 0.26 | 60 | None | .. |
| 56 | 40 | 0.26 | 40 | None | .. |
| 57 | 40 | 0.26 | 40 | None | .. |
| 58 | 35 | 0.21 | 90 | None | .. |

* Power density at the position of the exposed eye (i. e., at the 2-in. position).

† Disappeared within three to six months after irradiation.

Upon establishment of the threshold of Figure 1, the thermal characteristics of opacity formation were obtained from a second series of exposures. vitreous of the exposed eye at the posterior pole Temperature measurements were made in the of the lens by means of a thermistor. Shielding of the thermistor leads up to the point of entry into the eye permitted measurements to be made during the course of irradiation. Shielding was accomplished by means of a thin metal covering placed over the insulated lead wires. Body temperature measurements were made with a rectal thermometer. The results of the temperature measurements are shown in Figure 2.

## RESULTS

*Gross Ocular Pathology.*—Opacities occurred in 32 of the 58 rabbits subjected to 12.3 cm. radiation, as described in Table 1. An arbitrary classification into three groups was used for typing the damage observed.

(*a*) Minimal Opacities: These lesions appeared as clusters of small black dots in the region of the posterior suture of the lens and were probably not detrimental to vision. Eleven animals possessed lens damage of this type, previously described by Daily and associates.[4]

(*b*) Circumscribed Opacities: These lesions were roughly round or oval with sharp, dark borders, which often had a ray-like appearance, in contrast to the core, which was diffuse and less dense. These opacities were located in the region of the posterior horizontal suture; in two of the severe cases, the suture line separated the damage into upper and lower regions. Daily and associates[4] also reported similar observations. Some of the seven examples of this group appeared dense enough to interfere with vision.

(*c*) Diffuse, Irregular Opacities: This variable group of cataracts, obstructing vision, was comprised of large, opaque areas with peripheral crescents, dense linear projections, and vacuoles. In some cases the cataract involved the lens sufficiently to obscure the retina. Some change their shape during the 90-day observation period. Fourteen cataracts were included in this miscellaneous grouping.

All of the lens opacities produced in this study developed within 14 days after irradiation. Richardson and co-workers[5] found a similar period associated with repeated exposures, while with single exposures they observed a maximum time of nine days required for development. In this present work the minimal opacity required the longest time for development; the diffuse, the shortest, and the circumscribed, a period between

the two extremes. Thus, the degree of damage is inversely proportional to the time of appearance. In three cases minimal opacities regressed to the point of disappearance, but exposures producing these lesions were considered as having produced opacities.

Although the attention of this study was focused primarily on the production of opacities, other radiation effects were observed. High-power levels produced edema of the lid and conjunctiva. Enophthalmos, miosis, and injection of the conjunctiva occurred commonly. A few cases of retinal damage were noted, but in most cases lens opacities represented the severest damage which was grossly discernible. Exposures that caused prominent and persisting edema in the periorbital region resulted in cataracts of the greatest severity. Other secondary effects could not be satisfactorily correlated with the subsequent occurrence of opacities. Lens pathology is being accomplished and will be subsequently reported upon if warranted.

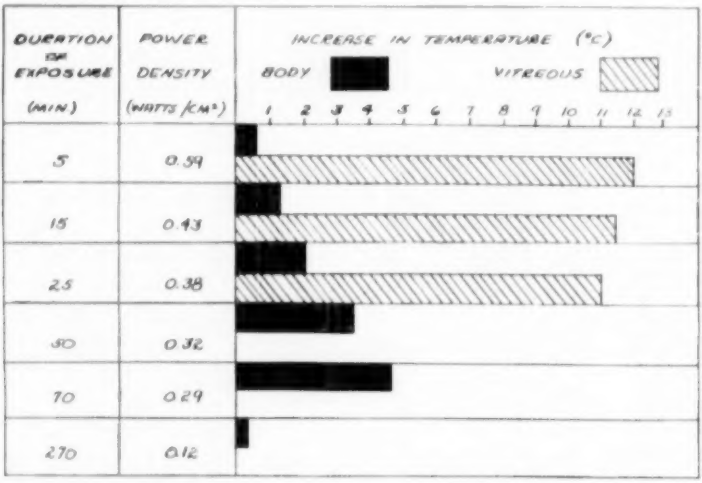



Fig. 2.—Increase in normal body and vitreous temperatures produced by ocular exposure to 12.3 cm. microwaves.

*Power and Time Thresholds of Opacity Formation.*—In order to delineate the time and power combinations which produce opacities, the data of Table 1 are presented graphically in Figure 1. Effective exposures are shown as crosses; ineffective episodes of exposure are indicated by circles. The solid line drawn through the experimental points represents an empirical limit above which production of lens opacities is a near certainty. The nature of this limit as a threshold is suggested by its passage through and proximity to experimental points which represent mixed results obtained by the same conditions of exposure. The significance of the threshold is not precisely known in terms of probability. It is of interest, however, that the empirical limit selected passes through approximately 25% of the total number of experimental points and effectively separates all of the remaining exposes except in one case.

In Figure 1, the threshold ranges from 5 minutes, at 0.59 watt/sq. cm., to 90 minutes, at 0.29 watt/sq. cm. One watt per square centimeter equals 14.3 cal/sq. cm/min. The threshold power densities, thus, are equivalent to a thermal flux of 8.4 to 4.1 cal/sq. cm/min., or doses of 42 to 369 cal/sq. cm. delivered during 5 to 90 minutes of exposure, respectively. Although power and energy units are interconvertible, as shown above, expression of the threshold power requirements in watts per square

centimeter appears adequate for the purposes of this report.

Compared at 10 minutes of exposure, the threshold power requirement of 0.48 watt/sq. cm. is only one-sixth of the 3 watts/sq. cm. which was regarded as hazardous by Salisbury and associates.[9] The extreme susceptibility of the eye to power densities greater than 0.4 watt/sq. cm. is indicated by the precipitous slope in this region. Below 0.4 watt/sq. cm. the rapidly decreasing slope of the threshold reflects the gross increase in the exposure time required for opacity production at only slightly lower power densities. Little is known of the threshold below 0.29 watt/sq. cm. except for exploratory exposures of 4.5 hours' duration at 0.22 and 0.12 watt/sq. cm., respectively. The production of severe ocular damage at 0.22 watt/sq. cm. is not typical of opacity production, as previously described. The extremely prolonged episode of ocular hyperthermia at 0.22 watt/sq. cm. permits time for the development of thermally induced, physiologic changes in the eye during the course of exposure. It is probable that these changes are not representative of the ocular system in which lens opacities are produced by relatively shorter periods of exposure at higher power densities. The failure of the 4.5-hour exposure at 0.12 watt/sq. cm. to elicit any discernible response suggests the proximity of a practical limit to power densities that can produce lesions of the lens by a single exposure under the conditions of the experiment.

*Temperatures Associated with Threshold Exposures.*—During the course of this investigation it became apparent that exposures of long duration produced a rise in whole-body temperature as measured rectally. This observation was made but not exploited by other investigators, who were concerned with relatively shorter periods of irradiation. Upon the development of the threshold described in Figure 1, a limited number of animals were exposed to threshold doses of radiation. In this latter experimental series, temperature measurements were made in the vitreous of the eye at the posterior pole of the lens, except as otherwise noted, and in the rectum during the course of each exposure. The results of these experiments, including a subthreshold exposure of 270 minutes at 0.12 watt/sq. cm., are summarized in Figure 2.

Increases in vitreous temperatures are indicative of the temperatures, ±2 C, which prevailed during most of the exposure episode at a given power density. Because of the deep level of anesthesia required to maintain the thermistor in the eye during prolonged periods of irradiation, satisfactory temperature measurements of the vitreous were not obtained for exposures in excess of 25 minutes. Moreover, considerable loss of vitreous around the thermistor lead was experienced during such protracted periods of irradiation.

Vitreous temperatures of between 53 and 49 C, respectively, are characteristic of threshold exposures between 5 and 25 minutes in duration. This level represents a 10 to 14 C elevation of vitreous temperature above normal and agrees well with the range of 51 to 55 C which was found significant in opacity production by Richardson and associates.[6]

Threshold exposures shorter than 25 minutes in length produced less than a 2 degree (C) rise in body temperature, whereas 50- to 70-minute threshold exposures at considerably lower power densities caused a 3 to 5 degree (C) increase in body temperature. In general it appears that the rise in body temperature is a direct function of the duration of threshold irradiation despite the higher power levels characteristic of brief exposures. These observations are in contrast to the results of subthreshold exposures at 0.12 watt/sq. cm., where a protracted period of exposure of 270 minutes produced a negligible body temperature elevation. Evidently at this latter power level the ability of the irradiated animal to dissipate heat is about equal to the energy flux on the head and eye.

Increases in body temperature decrease the quantity of power or the dose of radiation which is required to raise the tempera-

ture of the vitreous to the level of opacity production. The significance of even small decreases in the lens-damaging temperature differential through rises in body temperature is suggested by threshold cutaneous burn studies of Moritz and Henriques.[10] These investigators found that only 1 degree (C) increase in cutaneous temperature doubled the speed of reaction leading to thermal coagulation of cutaneous proteins in the temperature range of 44 to 51 C.

It is not within the scope of the present study to evaluate quantitatively the effect of increases in body temperature upon the threshold in terms of power requirements. An indirect measure of this effect, however, is obtained through a comparison of the 3 to 5 degree (C) elevation in body temperature with the 10 to 14 C temperature differential necessary to cause an opacity. In this case the threshold radiation dose is reduced by an amount corresponding to a 20% to 30% decrease in the temperature difference between the normal and the damaging vitreous temperature. The magnitude of this effect, which results from exposure of only the head, implies that a somewhat lower threshold would prevail where the body, as well as the head and eyes, was subjected to the thermal effects of 12.3 cm. radiation. Other heating effects, such as solar radiation, restricted air circulation, high relative humidity, high environmental temperatures, and, in general, any effects which tax the ability of the body to dissipate heat, are indicated as factors which would tend to lower the threshold requirements of opacity production. This effect would be particularly critical at low power densities which might not otherwise be capable of causing lens injury. Conversely, other conditions, such as low ambient temperature and low relative humidity, which would augment the ability of the body to dissipate heat, might well raise the threshold requirements of opacity production. Resolved in its simplest terms, the time and power threshold defined in the present study appear to be but one of a family of curves related by a third parameter, which represents a summation of environmental effects mentioned above.

## COMMENT

The clinico- and histopathology of microwave opacities is discussed in some detail elsewhere.¶ It appears worth while to mention, however, that the minimal opacities observed in this study have salient features in common with opacities described in rabbits subjected to ocular irradiation by x-, neutron- and beta-radiation.# This is particularly true in that vacuolar opacities induced by both 12.3 cm. microwaves and ionizing radiation show (1) a marked predilection for development in the region of the posterior horizontal suture, (2) a comparable latent period of onset (several days to several weeks), in the case of microwaves, and high doses of neutrons (14 mev) and beta-radiation, and (3) in some instances regression to the point of disappearance. The photon energy of 12.3 cm. radiation at $10^{-5}$ electron volts (thermal effects range) possesses only 1/3,000,000 of the 30 electron volts (ionizing effects' range) required for the production of a single ion pair. Thus, despite the fact that opacities induced by microwave and ironizing radiation are undoubtedly initiated by entirely different primary reactions (thermal *vs.* ionization), it may well be that these lesions, regardless of radiation type, become visible through a similar course of secondary events. A comprehensive study of lens changes produced by microwave *vs.* ionizing radiation might serve to elucidate the controversial features of the radiation cataract mechanism.

Because of its ready availability, the Raytheon Microtherm Director C was the instrument of choice in this as well as in other ocular studies. In the latter instances, the practice of relating biologic effects to the source-specimen exposure distance at a given total power output, rather than to the incident power density, has thus far prevented comparison of results obtained with this equipment. In the present study measurement of power density at the posi-

¶ References 3 and 4.

# References 11 to 13.

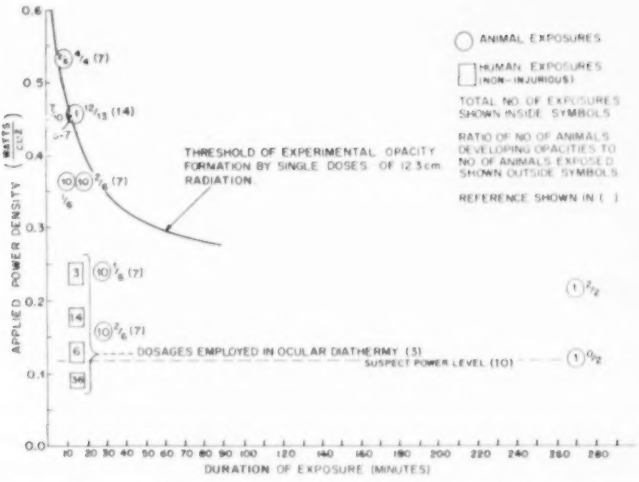

ANIMAL EXPOSURES
HUMAN EXPOSURES (NON-INJURIOUS)
TOTAL NO. OF EXPOSURES SHOWN INSIDE SYMBOLS
RATIO OF NO OF ANIMALS DEVELOPING OPACITIES TO NO OF ANIMALS EXPOSED SHOWN OUTSIDE SYMBOLS
REFERENCE SHOWN IN ( )
THRESHOLD OF EXPERIMENTAL OPACITY FORMATION BY SINGLE DOSES OF 12.3 cm. RADIATION.
DOSAGES EMPLOYED IN OCULAR DIATHERMY (5)
SUSPECT POWER LEVEL (10)
APPLIED POWER DENSITY (WATTS/CM²)
DURATION OF EXPOSURE (MINUTES)

Fig. 3.—Time and power densities significant in ocular irradiation with 12.3 cm. microwaves.

tion of exposure permits, for the first time, an expression of opacity formation in terms of the dose and dose rate responsible for its production. Calibration at other power output-distance combinations similarly provides information on the power densities which were used by investigators in otherwise comparable studies. Thus, a common basis is established for the integration of existing knowledge into a form which can give guidance to pertinent studies in the future. Such an integration has been performed in Figure 3, which graphically summarizes available knowledge on both human and animal ocular irradiation by microwaves. References for the data of Figure 3 are found in Tables 2 and 3.

*Human Irradiation.*—Although sufficiently high power levels may cause human ocular injury, lens damage has not been established as a radiation effect in humans. On the contrary, the thermogenic quality of 12.3 cm.

TABLE 2.—*Power Densities Employed by Various Investigators for Production of Experimental Opacities by 12.3 Cm. Microwaves* *

| Power Density,† Watt/Sq. Cm. | Distance from Deflector,‡ Inches | Exposures: Duration, Min. | No. | Periodicity | Opacity Production§ | Author Reference |
|---|---|---|---|---|---|---|
| | | Unanesthetized Rabbits Exposed at 94 Watts of Power Output | | | | Daily et al [4] |
| 0.53 | 2¼ | 10 | 2 | 1 every 20 days | 2/2 | |
| 0.53 | 2¼ | 10 | 6 | 1 every other day | 2/2 | |
| 0.36 | 3¼ | 10 | 10 | Daily | 1/6 | |
| 0.36 | 3¼ | 20 | 10 | Daily | 2/6 | |
| 0.24 | 4¼ | 30 | 10 | Daily | 1/6 | |
| 0.16 | 5¼ | 30 | 10 | Daily | 0/6 | |
| | | Anesthetized Rabbits Exposed at 94 Watts of Power Output | | | | Daily et al [4] |
| 0.16 | 5¼ | 30 | 10 | Daily | 2/6 | |
| | | Anesthetized Rabbits Exposed at 100 Watts of Power Output | | | | Richardson et al [3] |
| 0.46 | 2 | 15-20 | 1 | ..... | 12/13 | |
| 0.46 | 2 | 10-12 | 3-7 | ..... | 7/10 | |

* From the Raytheon Microtherm Director C diathermy apparatus.

† Approximate values derived from measurements of power density described in the Appendix to this report.

‡ Distance of exposure position as measured from the front surface of the plastic housing opposite and covering the dipole cross-over of Director C.

§ Ratio of the number of animals showing opacities to the number of animals exposed. Exposures according to Daily [4] have been grouped without regard to ocular pigmentation, which was not established as statistically significant in opacity production.

radiation has been used to advantage in ocular diathermy for treatment of the diseases of the posterior lens segment of the eye.[14] In this connection, it should be noted that the production of opacities in the present study is in no way intended to depreciate or

TABLE 3.—*Ocular Exposures Employed Clinically by Clark [14] in an Unusual Case* *

| Power Output, Per Cent | Power Density, Watt/Sq. Cm. | Exposures | | |
|---|---|---|---|---|
| | | Duration, Min. | No. | Periodicity (1960) |
| 20 | 0.09 | 15 | 36 | 1/23-7/27 |
| 30 | 0.13 | 15 | 6 | 7/28-8/24 |
| 45 | 0.18 | 15 | 3 | 7/28-8/24 |
| .. | .... | .. | 11 | 9/27-10/30 |
| 60 | 0.24 | 15 | 3 | 8/25-8/30 |

* Radiation source: Raytheon Microtherm Director C.

to discourage the use of the Microtherm where its use has been found desirable, but, rather, the purpose is to indicate limits which can give guidance for its successful application.

Although the threshold of experimental opacity production affords an estimate of power density which should be considered dangerous, its meaning in terms of human analogy has not yet been established. A better appraisal in this respect is obtained from consideration of the time and power parameters of exposures used in microwave diathermy of the human eye.

A standard ocular treatment reported by Clark [14] consisted of a 15-minute exposure of the open eye to 20% of the power output of the Raytheon Microtherm at a distance of 3 in. from Director C. In an unusual case it was possible to administer a number of exploratory exposures without fear of damaging an eye with already irretrievably lost sight. Although 23 of these exposures were at power levels considerably higher than the standard treatment, none of these exposures was deleterious. The approximate power densities employed in these treatments are shown as boxes in Figure 3.

It is notable that all of these exposures are at power levels well below the threshold for experimental opacity production. The standard clinical treatment employs only one-fourth the power density dose and dose rate that produces lens damage in the rabbit. Despite the production of severe ocular damage in the rabbit by 4.5 hours of exposure to 0.22 watt/sq. cm., it is of interest that three 15-minute exposures at this level were not injurious to the human eye. Human exposures at 0.24 watt/sq. cm. were discontinued because of pain or discomfort. Possible effects from protracted exposure at this power level are suggested by the massive ocular damage sustained by the rabbit from 4.5 hours of exposure to 0.22 watt/sq. cm. The production of sensible discomfort before injury to the human eye at 0.24 watt/sq. cm. is of interest in the light of a suggestion [9] that injury without warning may be caused by 12 cm. radiation in a region, such as the lens, that is poorly supplied with heat sensory receptors.

Hirsch and Parker [15] described a case in which exposure to microwaves is circumstantially linked to the occurrence of bilateral lenticular opacities in a microwave-generator operator. An etiologic relationship was not established in this case. The radiation source involved a 9 to 18 cm. wave generator with an average power output of about 100 watts on a 50%-duty cycle. The average daily level of exposure was believed to approximate 0.005 watt/sq. cm. It was estimated, however, that the operator's head was intermittently exposed to a power density of 0.12 watt/sq. cm. for a total of two hours during the three days preceding difficulty with vision.

It is of interest that the same power level of 0.12 watt/sq. cm. was found ineffective in rabbits receiving a single exposure as long as 270 minutes in duration. Additionally, it is notable that the suspect power level shown in Figure 3 is only slightly higher than the clinical level and is directly comparable to or lower than the power densities of 23 exploratory exposures which Clark gave without perceptible ill effect upon the lens.

*Cumulative Effects.*—There is a possibility that opacities may be produced as a cumulative radiation effect. Exploration of this contingency is of considerable importance

with respect to its connotations in human exposure to low-power levels of radiation over long periods of time. With the development of a threshold for experimental opacity production by a single exposure, it is expedient to examine the results of previous investigators for evidence of opacity formation as a cumulative effect of repeated exposures.

Irradiation parameters reported by Richardson,[5] and Daily [4] and their associates are shown as circles in Figure 3. The total number of exposures per rabbit eye are indicated inside the symbol. The ratio of the number of animals developing opacities to the total number of exposed animals is noted as a fraction between the circle and the author reference number in parentheses.

The 15- to 20-minute single-exposure requirement for opacity production as observed by Richardson and colleagues [5] at 100% power output corresponds to a power density of about 0.46 watt/sq. cm. Reference to Figure 4 (Appendix) confirms that this power density is within the power distribution at 2 in. from Director C of the Microtherm. The proximity of the multiple 10- to 12-minute exposures to the threshold suggests that any single exposure within this latter series may have produced lens damage without the need for additional exposures. Similarly, the results of Daily and associates [4] at 0.53 and 0.36 watt/sq. cm. are inconclusive with the exception of ten 10-minute exposures at the lower density, where one of six exposed animals sustained an opacity. An example more suggestive of opacity production as a cumulative effect is found in the ten 10-minute exposures at 0.16 and 0.24 watt/sq. cm. It is remarkable, however, that each of these latter densities are well below the threshold requirements for single exposures.

## SUMMARY AND CONCLUSIONS

Opacities can be produced in the eyes of anesthetized rabbits by single exposures to 12.3 cm. microwaves. Time and power requirements for experimental opacity formation ranges between 5 minutes, at 0.59 watt/sq. cm., and 90 minutes, at 0.29 watt/sq. cm. The power densities of this threshold correspond to a thermal flux of 8.4 to 4.1 cal/sq. cm/min. The trend of the threshold beyond 90 minutes is bracketed between 0.22 and 0.12 watt/sq. cm. for 4.5 hours of sustained irradiation. The failure of the protracted period of exposure at 0.12 watt/sq. cm. to cause any discernible effect suggests the proximity of a power density below which opacity production by this method is not practical.

As nearly as can be determined by ophthalmoscopic examination, all opacities are formed in the posterior lens segment and in some respects resemble lesions produced by certain ionizing irradiations. The quantity of 12.3 cm. radiation reflected and transmitted by the eye is unknown, but sufficient energy is absorbed to produce temperatures of 49 to 53 C at the site of the lens which later becomes cataractous. A latent period of 1 to 14 days elapses before the onset of discernible opacities. The lesions, in order of increasing severity, are classified according to appearance as minimal, circumscribed, and diffuse. Minimal lesions may not be detrimental to sight, but the last two types interfere with vision. Other ocular effects are observed but, for the most part, appear less significant than lens injury. Secondary effects are not consistently related to the development of lens damage except in some cases of the diffuse lesion, where severe and persisting periorbital edema appears to be a precursor of cataract formation.

Increases in body temperature are characteristic of exposure causing opacities. Despite the lower-power levels involved, higher body temperatures are associated with the longer periods of exposure. The indications are that the opacity threshold is partially a function of changes in body temperature and/or environmental factors that would affect the capability of the body for dissipating heat. The equivalent of the experimental threshold is not known in terms of human analogy. Consideration is being given the development of an opacity threshold in the monkey as an approach to the problem of extrapolation to

man. It is suggested in the interim, however, that the present threshold should be regarded as dangerous for human eyes until more definitive information is available. Limited evidence of opacity production as a cumulative effect from multiple subthreshold exposures emphasizes the need to explore further this aspect of ocular irradiation.

## APPENDIX

### Power Measurements on the Raytheon Microtherm Director C Combination [10]

*Generator Power Output.*—The power output of the Raytheon Microtherm, Model CDM4, was measured at 100% power meter setting. The equipment used for this purpose was comprised of a Hewlett Packard Microwave Power Meter, Model 430B, employed in conjunction with a Hewlett Packard Tunable Bolometer, Mount Model 475B. A calibrated length of RG-21/4 was used between the input of the H. P. M. P. Meter and the output of the Microtherm. The attenuation of the cable was 55.00 db. One hundred per cent output of 93.8 watts was calculated from the H. P. M. P. Meter reading according to the mathematical definition of power attenuation in decibels:

$$\text{db} = \log \frac{\text{power (input)}}{\text{power (output)}} \quad (1)$$

where power input=P. H. M. P. Meter reading in watts. This particular Microtherm was rated by the manufacture,[10] at approximately 95 watts of power output at the same setting.

*Antenna Power Output.*—The intensity of the radio frequency field from Director C of the Microtherm was measured. The same power-measuring equipment was used, but with an attenuation of 26.34 db. between the power-measuring equipment and the dipole pick-up antenna. The effective area of the pick-up antenna was 21.3 sq. cm. at 2450 mc. Power measurements were made with the dipole pick-up antenna positioned in space at distances up to 7 in. from the Director. Distances were measured from the plane coincident with the anterior surface of the plastic housing which covers the dipole cross-over of Director C. Measured power in watts was converted to field strength in the same units by means of the following expression, which is readily derived from Equation 1.

$$\text{Field strength} = \text{H. P. M. P. Meter reading} \times \text{antilog} \frac{\text{attenuation}}{10} \quad (2)$$

where attenuation is expressed in decibels. Field-strength values were converted to power densities in watts per square centimeter according to the expression:

$$\text{Power density} = \frac{\text{Field strength}}{A_{eff}} \quad (3)$$

where $A_{eff}$ refers to the effective surface area of the dipole pick-up antenna in square centimeters.

Power measurements were primarily concerned wtih evaluating the field strength at the 2-in. position which was used for ocular exposures in the present study. Additional measurements at other distance-power combinations were made in order to obtain an estimate of the power densities employed by earlier investigators. Figure 4 shows the power distribution in a 3×4 in. cross section of the beam at the 2- and 3-in. positions. The data are reported to the nearest 0.1 watt/sq. cm. and were obtained at 100% power output. Figure 5 reflects field strength as a function of distance from the deflector. These latter values were obtained in space directly opposite the Microtherm dipole cross-over at power levels and distances indicated within

Table 4.—*Power Density as a Function of Microtherm Power-Meter Setting*

| Microtherm Power-Meter Setting Per Cent Power Output | Calculated Power Density,* Equations 2 and 3 | Watt/Sq. Cm. Equation 4 |
|---|---|---|
| 10 | 0.10 | 0.10 |
| 20 | 0.14 | 0.15 |
| 30 | 0.22 | 0.21 |
| 35 | .... | 0.24 |
| 40 | 0.26 | 0.26 |
| 45 | .... | 0.29 |
| 50 | 0.33 | 0.32 |
| 55 | .... | 0.35 |
| 60 | 0.39 | 0.38 |
| 65 | .... | 0.40 |
| 70 | 0.43 | 0.43 |
| 75 | .... | 0.46 |
| 80 | 0.49 | 0.48 |
| 85 | .... | 0.51 |
| 90 | 0.54 | 0.54 |
| 100 | 0.58 | 0.59 |

* Average deviation ±20% at 0.1 watt/sq. cm. to ±4% at 0.58 watt/sq. cm.

All measurements were taken in space directly opposite the dipole cross-over and at a distance of 2 in. from the anterior surface of the plastic covering on the dipole assembly.

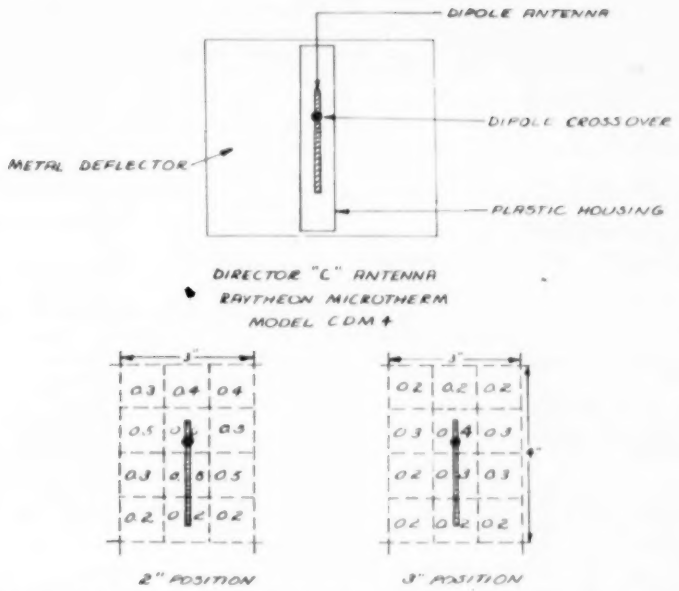



Fig. 4.—Power distribution in the beam at 2- and 3-in. distance from Director C of the Raytheon Microtherm operating at 100% of power output. Power densities are reported to the nearest 0.1 watt/sq. cm.

the Figure. This region of the beam cross section was consistently found to possess the maximum power density at distances up to 7 in.

Power densities at the 2-in. position and directly opposite the dipole cross-over are shown in Table 4, Column 2, as a function of the Microtherm power-meter setting. According to the method of least mean squares, these data are readily expressed by the equation:

$$\text{Power density} = 0.0456 + 0.00547 \times \text{Microtherm power-meter setting} \quad (4)$$

where power density is expressed in watts

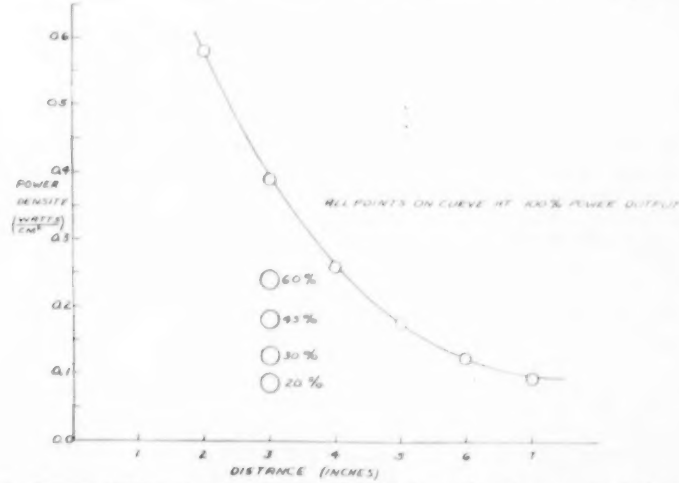



Fig. 5.—Power density as a function of distance from the Director C of the Raytheon Microtherm.

per square centimeter and the power-meter setting is in per cents of power output. The agreement between power densities normalized with the aid of Equation 4 and calculated by Equations 2 and 3 is reflected by a comparison of Columns 2 and 3 of Table 4.

Col. E. A. Pinson, Mr. N. Bouymaster, and Drs. D. G. Cogan, J. F. Herrick, H. M. Hines, and F. G. Hirsch made helpful suggestions. The Raytheon Mfg. Company loaned the equipment used in this study.

REFERENCES

1. Brody, S. I.: The Operational Hazard of Microwave Radiation, J. Aviation Med. **24**:328-333 (Aug.) 1953.

2. Clark, J. W.: Effects of Intense Microwave Radiation on Living Organisms, Proc. Inst. Radio Engin. **38**:1028-1032 (Sept.) 1950.

3. Daily, L., Jr.; Wakim, K. G.; Herrick, J. F.; Parkhill, E. M., and Benedict, W. L.: Effects of Microwave Diathermy on the Eye, Am. J. Ophth. **33**:1241-1254 (Aug.) 1950.

4. Daily, L., Jr.; Wakim, K. G.; Herrick, J. F.; Parkhill, E. M., and Benedict, W. L.: Effects of Microwave Diathermy on the Eye of the Rabbit, Am. J. Ophth. **35**:1001-1017 (July) 1952.

5. Richardson, A. W.; Duane, T. D., and Hines, H. M.: Experimental Lenticular Opacities Produced by Microwave Irradiations, Arch. Phys. Med. **29**:765-769 (Dec.) 1948.

6. Herrick, J. F., and Krusen, F. H.: Certain Physiologic and Pathologic Effects of Microwaves, Electrical Engin. **72**:239-244 (March) 1953.

7. Hines, H. M., and Randall, J. E.: Possible Industrial Hazards in the Use of Microwave Radiation, Electrical Engin. **71**:879-881 (Oct.) 1952.

8. Richardson, A. W.; Duane, T. D., and Hines, H. M.: Experimental Cataract Produced by Three-Centimeter Pulsed Microwave Irradiations, A. M. A. Arch. Ophth. **45**:382-386 (April) 1951.

9. Salisbury, W. A.; Clark, J. W., and Hines, H. M.: Exposure to Microwaves, Electronics **22**: 66-67 (May) 1949.

10. Moritz, A. R., and Henriques, C. F., Jr.: Studies of Thermal Injury: II. The Relative Importance of Time and Surface Temperatures in the Causation of Cutaneous Burns, Am. J. Path. **23**:695-720 (Sept.) 1947.

11. Cogan, D. G., and Donaldson, D. D.: Experimental Radiation Cataracts: I. Cataracts in the Rabbit Following Single X-Ray Exposure, A. M. A. Arch. Ophth. **45**:508-522 (May) 1951.

12. Cogan, D. G.; Goff, J. L., and Graves, E.: Experimental Radiation Cataracts: II. Cataracts in the Rabbit Following Single Exposure to Fast Neutrons, A. M. A. Arch. Ophth. **47**:584-592 (May) 1952.

13. McDonald, J. E.; Hughes, W. F., Jr., and Peiffer, V. G.: Beta Radiation Cataracts, A. M. A. Arch. Ophth. **53**:248-259 (Feb.) 1955.

14. Clark, W. B.: Microwave Diathermy in Ophthalmology: Clinical Evaluation, Tr. Am. Acad. Ophth. **56**:600-607 (July-Aug.) 1952.

15. Hirsch, F. G., and Parker, J. T.: Bilateral Lenticular Opacities Occurring in a Technician Operating a Microwave Generator, A. M. A. Arch. Indust. Hyg. **6**:512-517 (Dec.) 1952.

# News and Comment

## SOCIETY NEWS

**Florida Midwinter Seminar.**—The Tenth Annual Meeting of the University of Florida Midwinter Seminar in Ophthalmology and Otolaryngology will be held at the Sans Souci Hotel in Miami Beach the week of Jan. 16, 1956. The lectures on ophthalmology will be presented on Jan. 16, 17, and 18, and those on otolaryngology, on Jan. 19, 20, and 21. A midweek feature will be the midwinter convention of the Florida Society of Ophthalmology and Otolaryngology on Wednesday afternoon, Jan. 18, to which all registrants are invited. The registrants and their wives may also attend the informal banquet at 8 p. m. on Wednesday. The schedule has been changed to provide a maximum time for recreation each afternoon.

The Seminar lecturers on ophthalmology this year are Dr. Francis H. Adler, Philadelphia; Dr. A. Gerard DeVoe, New York; Dr. Michael J. Hogan, San Francisco; Dr. C. Wilbur Rucker, Rochester, Minn., and Dr. A. D. Ruedemann, Detroit. Those lecturing on otolaryngology are Dr. Frederick A. Figi, Rochester, Minn.; Dr. Lewis F. Morrison, San Francisco; Dr. Charles E. Kinney, Cleveland; Dr. John E. Lindsay, Chicago, and Dr. Bernard J. McMahon, St. Louis.

# Hysterical Amblyopia

## Statistical Analysis of Forty-Two Cases Found in a Survey of Eight Hundred Unselected Eye Patients at a State Medical Center

T. F. SCHLAEGEL Jr., M.D., Indianapolis
and
F. V. QUILALA, M.D., Quezon City, Philippines

Because of the clinical impression that hysterical amblyopia, when specifically looked for, is commoner than is generally believed; and because the incidence, as determined by a review of the literature, cannot properly be evaluated in terms of the subtler cases, it seemed that a clinical reexamination of this problem could be profitable. It is the purpose of this study to determine by survey, using perimetric methods, the actual incidence of hysterical amblyopia in a large group of unselected eye patients.

There have been many individual reports * of cases of hysterical amblyopia and amaurosis, but series of any size, with statistical studies, are conspicuously lacking in the literature.

### MATERIALS AND METHODS

Eight hundred unselected eye patients, with various complaints and diagnoses, were examined. The routine examination for the purpose of this study was as follows: Visual acuity was taken without and with glasses. If glasses improved the vision by as much as one line, the patient was examined perimetrically with glasses on.

The examination was standardized for all patients as follows: The tangent screen test was explained to the patient. The fixation point for patients with normal vision was a gray disc, 1 cm. in diameter, with a black-headed pin at the center. For those with poorer vision, white discs, of increasing size, held by a black pin, were used. The patient was seated on a stool with his head fixed in a chin rest. The right eye was tested first unless the vision in that eye was less than that of the left eye. A trial run on the blind spot was done to instruct the patient and to demonstrate the method. The examination was done at 2 meters from the screen, using a 10 mm. white test object. The test was started on the temporal side of the horizontal meridian. The test object was moved in from the blind to the seeing area. Subsequent radii at intervals of 30 degrees were tested, the test being conducted around the screen in a clockwise manner.

After the two eyes had been examined separately at 2 meters, the patient was moved up to 1 meter from the screen and the test repeated, with use of a 5 mm. white test object to provide a constant angular size.

After the perimetric examination, the corneal sensitivity of each eye was tested with a sterile cotton wisp as the patient fixed his gaze straight ahead. The patient's lids were held open, and the wisp of cotton was brought in from the temporal side, out of the field of vision, to touch the cornea. If the patient made no lid response and claimed no feeling, the corneal sensitivity was graded 0. If the patient made no response but said he did feel something vaguely, the sensitivity was graded 1. When there was lid response and/or a definite sensation of touch, the sensitivity was graded 2. Lacrimation and/or a definite sensation of discomfort was graded 3, and a complaint of pain and withdrawing movement of the head, 4.

If the patient was found to have tubular or spiral fields, perimetric examination was done, using a Ferree-Rand perimeter. A 3 mm. white test object was used at 330 mm. Two weeks later the patient was reexamined on the tangent screen. If the result was still positive, another examination was made after a lapse of two more weeks. On this third visit the method of testing was reversed in three of its details: (1) The left eye was tested first; (2) the test object was moved centrifugally (from the seeing to the blind area), and (3) the test was conducted in a counterclockwise, rather than a clockwise, manner.

Received for publication Sept. 19, 1955.

From the Department of Ophthalmology, Indiana University School of Medicine.

This study was supported by the James Whitcomb Riley Memorial Association. Dr. Frank Miller participated in the early part of this study.

* References 1 to 113.

After 275 of the 800 patients had been tested, the confrontation test was added to the study of the last 525. This was used as a preliminary test to other field studies to determine whether this simple test could serve as a reliable screening technique. The confrontation test was done with moving fingers brought centripetally from the blind to the seeing area. If contraction was obtained, the test was repeated after roughly doubling the distance from the patient.

## RESULTS

A total of 800 patients attending the Eye Clinic of the Indiana University Medical Center were examined for the purpose of this study. Since a number of these patients came from the State Prison, Reformatory, Boys' School, and Women's Prison, and therefore were possibly subject to environmental selection, with a higher incidence of psychogenic disorders and malingering than noninstitutional patients, they were grouped separately. Of the 800 patients, 135 were institutional and 665 noninstitutional cases.

1. *Incidence of Tubular Fields.*—Forty-two tubular fields were found among the 800 patients of this study (5.25%). Ten of the 135 institutional cases (7.40%) and 32 of the 665 noninstitutional cases (4.81%) had tubular fields (Table 1).

2. *Role of Sex in Incidence of Tubular Fields.*—The incidence of tubular fields was higher among female than among male patients, both among the institutional and the noninstitutional cases, although the statistical significance did not quite reach the 0.05 level (Table 1).

3. *Corneal Sensitivity in Patients with Tubular Fields.*—Corneal sensitivity was significantly lower among the patients with

TABLE 2.—*Corneal Sensitivity of 800 Unselected Eye Patients Divided into Five Grades, from No to Maximum Objective Response, as Found in Controls and in Patients with Tubular and Spiral Fields*

| | Control | | Tubular | | Spiral | |
|---|---|---|---|---|---|---|
| Grade* | No. | Per Cent | No. | Per Cent | No. | Per Cent |
| 0 | 6 | 0.80 | 3 | 7.14 | 2 | 11.11 |
| 1 | 228 | 30.44 | 27 | 64.29 | 6 | 33.33 |
| 2 | 453 | 60.48 | 12 | 28.57 | 10 | 55.56 |
| 3 | 59 | 7.88 | 0 | 0.00 | 0 | 0.00 |
| 4 | 3 | 0.40 | 0 | 0.00 | 0 | 0.00 |
| Total | 749† | 100.00 | 42† | 100.00 | 18† | 100.00 |

* 0 indicates none; 4, maximum response.
† Apparent discrepancy due to the fact that some cases were both tubular and spiral.

TABLE 3.—*Frequency of Tubular Fields Grouped According to Severity of Contraction*

| Grade with Range, Degrees | No. | Per Cent |
|---|---|---|
| Mild (21°-30°) | 4 | 9.52 |
| Moderate (11°-20°) | 16 | 38.10 |
| Severe (0-10°) | 22 | 52.38 |
| Total | 42 | 100.00 |

TABLE 4.—*Age Distribution of Control and Tubular Fields Grouped into Five Age Periods and Given in the Form of Numbers and Percentages*

| | Age, Yr. | | | | | |
|---|---|---|---|---|---|---|
| | 5-19 | 20-34 | 35-49 | 50-64 | 65-79 | Total |
| Control fields | 259 | 243 | 106 | 90 | 47 | 745 |
| | 35% | 33% | 14% | 12% | 6% | 100% |
| Tubular fields | 14 | 9 | 5 | 11 | 3 | 42 |
| | 33% | 22% | 12% | 26% | 7% | 100% |

TABLE 5.—*Laterality of Tubular Fields*

| | No. | Per Cent |
|---|---|---|
| Unilateral | 1 | 2.4 |
| Bilateral | 33 | 78.6 |
| Other | 8 | 19.0 |
| Total | 42 | 100.0 |

TABLE 1.—*Sex Distribution of Tubular, Control, and Other Fields as Found in a Survey of 800 Unselected Eye Patients Divided into Institutional and Noninstitutional Cases*

| | | Tubular | | Control | | Other Fields | |
|---|---|---|---|---|---|---|---|
| | | No. | Per Cent | No. | Per Cent | No. | Per Cent |
| Institutional cases (135) | Males (124) | 8 | 6.45 | 112 | 90.32 | 4 | 3.23 |
| | Females (11) | 2 | 18.18 | 8 | 72.73 | 1 | 9.09 |
| | | 10 | 7.40 | 120 | 88.88 | 5 | 3.72 |
| Noninstitutional cases (665) | Males (290) | 7 | 2.41 | 282 | 97.24 | 1 | 0.35 |
| | Females (375) | 25 | 6.66 | 347 | 92.53 | 3 | 0.81 |
| | Both sexes (665) | 32 | 4.81 | 629 | 94.59 | 4 | 0.60 |
| Total (800) | Both sexes | 42 | 5.25 | 749 | 93.62 | 9 | 1.13 |

TABLE 6.—*Effect of Method of Taking the Visual Field on Size of the Tubular Field Obtained* *

| Patient No. | Difference, in Degrees, Between First and Second Visit | Difference, in Degrees, Between Second and Third Visits |
|---|---|---|
| 1 | −4 | +6 |
| 2 | +8 | −2 |
| 3 | +14 | −5 |
| 4 | 0 | 0 |
| 5 | +9 | 0 |
| 6 | −7 | +5 |
| 7 | −3 | 0 |
| 8 | −2 | +2 |
| 9 | 0 | 0 |
| 10 | 0 | 0 |
| 11 | 0 | 0 |
| 12 | 0 | +3 |
| 13 | −5 | 0 |
| 14 | 0 | 0 |
| 15 | 0 | 0 |
| 16 | +4 | +6 |
| Total | +14 | +15 |
| Mean | +0.88 | +0.94 |

* The change in size of the tubular field as measured at 1 meter between the first and the second visit, when the same technique was employed, as compared with the change in size between the second and the third visit, when the technique was altered.

TABLE 7.—*Type and Incidence of Organic Eye Disease in Patients with Tubular Fields*

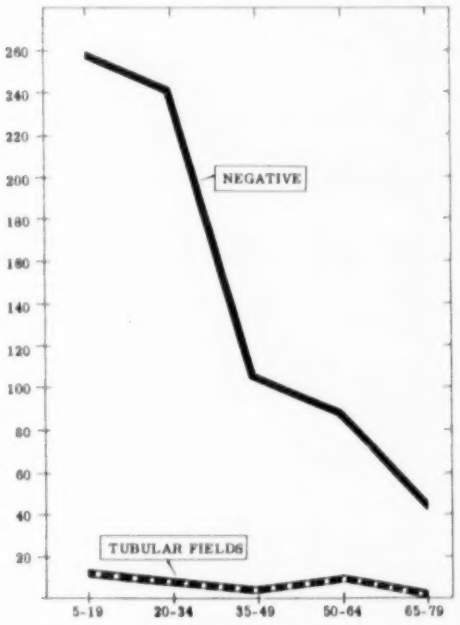
| Condition | Incidence |
|---|---|
| Cataract | 4 |
| Diabetes | 2 |
| Uveitis | 4 |
| Macular plaque | 1 |
| Glaucoma | 1 |
| Keratitis neuroparalytica | 1 |
| Esotropia | 1 |
| Drusen retinae | 1 |
| Enucleation of opposite eye | 1 |
| Burn of cornea | 1 |
| Total | 17 (15 patients) |
| Undetermined | 4 |
| None | 23 |
| Grand total | 42 |

TABLE 8.—*Best Corrected Visual Acuity of Tubular Cases*

| Visual Acuity | No. of Tubular Field Cases |
|---|---|
| 20/15 | 3 |
| 20/20 | 17 |
| 20/25 | 5 |
| 20/30 | 4 |
| 20/40 | 3 |
| 20/50 | 1 |
| 20/60 | 2 |
| 20/70 | 1 |
| 20/100 | 1 |
| 20/200 | 4 |
| 20/400 | 1 |
| Total | 42 |

tubular fields ($p<0.001$) (Table 2), but this lack of corneal sensitivity was not a striking feature of individual cases.

4. *Degree of Contraction of Tubular Fields.*—Tubular fields were grouped according to the degree of contraction as measured at 1 meter: mild (21 to 30 degrees), moderate (11 to 20 degrees) and severe (0 to 10 degrees). In the majority of cases (52.38%) the fields were severely contracted (0 to 10 degrees; Table 3). The most frequently observed size was 10 degrees. Ten, or 23.8%, of the 42 cases of tubular fields had a radius of 10 degrees when measured at 1 meter. The mean size of the tubular fields was 11.3 degrees; the median, 9+ degrees; the mode, 10 degrees; the range, 2-25 degrees.




Number of normal or negative visual fields compared with the number of tubular fields at various age periods; the incidence of tubular fields (in relation to the number of patients) is significantly increased at the age period of 50 through 64 years.

5. *Role of Age in Incidence of Tubular Fields.*—The age distribution of our controls and tubular fields was also studied (Table 4; Figure 1). In the population which we

studied the incidence of tubular fields is significantly increased in the age group of 50 to 64 years. In this age group, 11 of a total of 101 patients, or over 10% of the patients seen at ages of 50 to 64, had the tubular fields of hysteria. The $\chi^2$ test, with Yates' correction, gave a $p<0.02$.

The apparent decrease in the incidence of tubular fields from 20 to 34 years of age (Table 4) did not prove to be significant ($p<0.20$).

6. *Laterality of Tubular Fields.*—Only 1 (2.4%) of the 42 tubular fields was strictly unilateral; 33 (78.58%) were bilateral (Table 5). The remaining eight cases consisted of 5 patients with only one eye, 2 patients with one eye with tubular and the other with spiral fields, and 1 patient with both eyes presenting spiral fields of a tubular character.

7. *Effect of Method of Taking Visual Fields.*—Since much has been written about tubular fields being suggested into being by the examiner, these patients with tubular fields who returned for their third visit were tested differently in three details of the examination. The left eye was tested first and in a counterclockwise direction, and the test objects were moved centrifugally from the seeing to the blind area. Of the 42 tubular field patients, only 16 returned for their third visit. In an attempt to determine whether the change in the tubular fields obtained, we have compared the change in contraction of the tubular fields in the same patients from the first to the second visit, when the same technique was used, with the change from the second to the third visit, when the technique of taking the visual fields was altered.

Table 6 demonstrates no significant difference between the results when the same and when altered technique was used.

8. *Reliability of the Confrontation Test for Detecting Tubular Fields.*—The diagnosis made by the confrontation test was confirmed in every instance by the subsequent tangent screen and perimetry studies. No false-positive or false-negative results were obtained. Spiral or organic field defects gave contraction of the visual fields, but these were not tubular in character when checked at a greater distance. Of the first 275 patients checked for tubular fields without a preliminary survey by the confrontation method, 11 (4.0%) were found to have tubular fields. Of the last 525 patients with whom the confrontation method was used, 31 (5.9%) were found to have tubular fields. In $\chi^2$ calculations no significant difference between the 4.0% and 5.9% values were revealed.

9. *Duration of Tubular Fields.*—The patients in this study were not followed for a sufficient period to permit an adequate answer to this question.

10. *Concomitant Organic Factors in Patients with Tubular Fields.*—In Table 7 it can be seen that various types of organic conditions were found among the patients with tubular fields. Thus, the presence of some organic ocular condition does not preclude the presence of the tubular fields of hysteria. Of the 42 tubular field patients, 15 (35.7%) had concurrent organic ocular conditions. Most of the remainder had presented themselves for refraction.

11. *Presenting Complaint of Patients with Tubular Fields.*—A wide variety of complaints was encountered. It is interesting that nine had no complaints referable to the eyes. The commonest presenting symptom was decreased visual acuity, and the next commonest was eyestrain. None complained of a restricted field of vision.

12. *Visual Acuity of Tubular Field Patients.*—From Table 8 it can be seen that 20 (48%) of the 42 tubular field patients had a corrected vision of 20/20 or better and only 44.7% had a vision of 20/30 or less. There was no correlation between visual acuity and the degree of contraction of the tubular fields.

## COMMENT

*Diagnosis.*—Hysterical amblyopia is diagnosed by the presence of tubular fields. Nothing but hysteria (unless it be malinger-

ing) will produce tubular fields, and its signs are classic and easily recognized.

1. First, and most important, the fields are the same size no matter at what distance they are checked. The visual fields may be checked at 0.5 or at 4 meters, and the size will remain essentially constant.† It may increase or decrease slightly, but within only a narrow range.

2. Tubular fields have sharp borders. A 1 mm. bead or an 8½×11 in. sheet of paper will give almost identical isopters.[105]

3. Tubular fields are typically circular in shape, as though drawn by a compass. They do not demonstrate the normal widening to the temporal side. By definition, any field which is not circular or tubular in character is not a tubular field. However, the diagnosis of other types of hysterical fields, which do not assume a tubular shape, may be made from the first two criteria, which are the important ones.

4. The diagnosis should be hysteria, and not malingering, until proved otherwise. Hysteria is much commoner than malingering, even in prisons and the armed services. Hysterics may give positive results on some of the malingering tests; so one must not place too much faith in them. The differential diagnosis is usually easily made on the basis of general features. The hysteric is usually more indifferent and nonchalant than normal, whereas the malingerer usually overplays his part.[53] The patient with tubular fields is unconscious of any constriction of his field of vision. The reason for this is that he sees unconsciously in the hysterically blind periphery and therefore navigates a crowded room without bumping into objects. The malingerer is "blinder than the b'ind." Charlin published photographs demonstrating how a blind man will look directly at a person with whom he is conversing, whereas a malingerer will take pains to avert his head and eyes.[54] The hysteric usually enjoys the examination, whereas the malingerer is resentful and sulky. The malingerer will do nothing for himself. He often has signs of traumatic conjunctivitis or keratitis.[53] Hysterical amblyopia is usually bilateral, while the malingerer simulates loss of vision usually on only one side.

5. The use of color fields is complicated, time-consuming, and unnecessary.

6. Hysterical amblyopia may overlay organic disease, so that the diagnosis must not be made by exclusion but must be based on its characteristic diagnostic features.

7. A provisional diagnosis can be made in a few seconds by the confrontation test. If the field is not contracted, it is not tubular. If it is contracted, one should move back several steps and repeat the test. If the fields are contracted (usually to about 1 ft. in diameter) and of the same size for the two distances, the diagnosis is tubular fields until proved otherwise.

*Incidence of Tubular Fields.*—Rowland and Rowe[51] found 100 cases of marked concentric contraction of the visual fields in a study of 1900 inpatients. This is an incidence of 5.26%—a figure almost identical with the 5.25% incidence of tubular fields found in this study. Rowland and Rowe apparently did not consider the tubular fields of hysteria, although the majority of their cases were undoubtedly of this type.

Eames[99] examined 193 unselected school children for tubular fields. His criterion was concentric contraction to 15 degrees or less, which fails to take into account the sharp borders and tubular character of tubular fields. He found an incidence of 9%.

The best work on hysterical amblyopia in recent years has been done by Yasuna. In 1946 he reported on 15 cases seen at a Separation Center.[97] The incidence was just over 1%. In 1951 he reported on 19 additional cases but was unable to give the incidence, since some selection was involved in that patients with such trouble had been referred to him.[109] In our present study, patients with tubular fields who were referred to us with that diagnosis were not included in this study.

† References 55 and 105.

We found that 7.40% of our institutional cases and 4.81% of our noninstitutional cases had tubular fields. These frequencies were obtained by making a routine and thorough study of 800 unselected eye patients at the Indiana University Medical Center. The incidence of tubular fields in the private practice of ophthalmology does not appear to be nearly this high, but it certainly is not a rare condition.

*Role of Sex in the Incidence of Tubular Fields.*—Yasuna found that of his 19 cases of hysterical amblyopia, 13 were female and 6 male. This conforms with our experience. In our noninstitutional group, tubular fields were more than twice as common among females. The previous reports of Utgoff, Krone, and Brikke (cited by Gurvitch [69]) also support the much greater incidence of tubular fields among females.

*Corneal Sensitivity in Patients with Tubular Fields.*—Although corneal anesthesia has long been considered a characteristic of hysteria, there is a difference in opinion as to its incidence. Miller [94] found bilateral corneal anesthesia in 17 of 19 soldiers with the diagnosis of psychoneurosis hysteria. In another group, of 50 men with hysteria, 47 had bilateral corneal anesthesia. Halpern [86] found that 14 of his 15 cases of hysterical amblyopia had corneal reflexes. Yasuna [109] found the corneal reflex diminished in only 2 of his 19 cases. An explanation for these differences of opinion in the literature may be had by reference to Table 2. Only 3 of our 42 cases of hysterical amblyopia had absent corneal reflexes. Absence of the corneal reflex was also seen in our control fields and in those patients with spiral fields. In our experience, an absent or diminished corneal reflex was not a striking feature of individual cases of tubular fields. It is true that corneal sensitivity of the group of tubular field patients was significantly reduced when compared with the control group (calculated by the $\chi^2$ method). In the majority of the tubular field patients in our study the corneal sensitivity was significantly reduced, but not necessarily absent. It thus appears that the differences of opinion found in the literature may be due to a difference in criteria for presence or absence of corneal anesthesia.

*Degree of Contraction of Tubular Fields.*—Yasuna found tubular fields to vary in size between 1 and 35 degrees; our range was from 2 to 25 degrees. Of Halpern's cases, two-thirds had concentric tubular contraction below 20 degrees. The commonest-size tubular field is about 10 degrees when measured at 1 meter, and most of the cases will fall around this area (Tables 3 and 9).

*Role of Age in Incidence of Tubular Fields.*—Of Yasuna's [109] 19 patients, 8 were from 9 through 13 years of age, but he had no information regarding the age of the population from which his patients were drawn. The studies done by workers in the armed services are also of little help to us because of the selected population. Foster Moore [85] saw three patients with hysterical blindness under the age of 8 years. Since it is difficult to determine visual fields on young children, we did not check them under the age of 5 years, and checked very few in the routine eye patients under the age of 8. Our youngest patient with tubular fields was 7 years old.

TABLE 9.—*Degree of Contraction of Tubular Fields*

| Author | Range, Degrees | Median, Degrees | Mean, Degrees | Mode, Degrees |
|---|---|---|---|---|
| Yasuna [109] | 1-35 | .. | .... | .... |
| Eames [99] | .... | 9 | .... | .... |
| Schlaegel and Quilala | 2-25 | 9+ | 11.3 | 10.0 |

Krone (cited by Gurvitch [69]) saw 20 cases in the second decade, 15 cases in the third decade, 6 cases in the fourth decade, 2 cases in the fifth decade, and only 1 case in the sixth decade of life. Utgoff (cited by Gurvitch [69]) found that 72% of his cases were found in patients up to 30 years of age. From our reading and previous experience we had been under the impression that hysterical amblyopia was commonest in children and young adults and were surprised to discover that the age group with the greatest incidence of tubular fields was the 50- through

the 64-year age period. We, apparently, were the first to run a control group and subject our findings to statistical analysis. The reason for the misconception that we had is well demonstrated in the Figure, where it can be seen that the largest number of patients with tubular fields was in the 5- to 19-year age period, but the control curve shows that there were more eye patients of all types in this age category. It was only when we calculated percentages and conducted statistical analyses that we found that the only age period during which there was a significant increase or decrease in the incidence of tubular fields over that at other ages was the 50- to 64-year age group, and at these ages tubular fields were commoner than at any other age period.

*Reliability of the Confrontation Test for Detecting Tubular Fields.*—The incidence of tubular fields found in the eye patients of this series was not increased by the possible suggestive effect of the confrontation test. We have found the confrontation test to be a rapid and reliable screening test for tubular fields. Equivocal cases should be subjected to tangent screen studies.

*Visual Acuity of Tubular Field Patients.*—Eames[39] found that 44% of his cases of tubular fields exhibited an amblyopia sufficient to reduce their visual acuity to 20/30 or less. In our series, 44.7% of our patients had a visual acuity of 20/30 or less (Table 8). Thus, reduced central acuity is not an invariable associate of tubular fields. It would appear that the term hysterical amblyopia frequently is not applicable. Yasuna found that two-thirds of his patients had an initial visual acuity of 20/100 or 20/200. However, after suggestion the corrected vision was improved to 20/30 or 20/40, and in some instances to 20/20. In most of our patients the visual acuity was recorded after a refraction, when suggestion tends to secure an improved visual acuity. We found, as did Yasuna,‡ that the reading of the chart was typically slow and deliberate, with long pauses between letters, whether the 20/100 or the 20/30 line was being read. Changing lenses, without any change in dioptric power, will enable these patients to read down a little farther on the chart.

‡ References 97 and 109.

## SUMMARY

The tubular fields of hysteria are easily diagnosed from the following criteria:

(*a*) The fields are of the same size no matter what the distance.

(*b*) The borders are very sharp.

(*c*) The field is circular.

The confrontation method is a quick and reliable screening technique.

The method of taking the visual field appears to play no role in the incidence of tubular fields.

Tubular fields are not rare. The incidence in this study was 5.25% of eye patients.

Tubular fields are common in patients with organic eye disease.

Corneal sensitivity is reduced in tubular field patients but is not a reliable diagnostic sign.

The tubular fields observed in this study varied from 2 to 25 degrees but were most commonly 10 degrees in radius when measured at 1 meter.

Contrary to popular belief, the tubular fields in our series were commonest between the ages of 50 and 64.

Reduced visual acuity was the commonest presenting complaint, but some had no eye complaint.

Although amblyopia is commonly associated with tubular fields, the visual acuity as a result of refraction was 20/20 or better in 48% of our cases. The vision is frequently easily improved by such suggestion and encouragement.

## BIBLIOGRAPHY

1. Lepois, C.: 1618; cited by Parinaud.[13]

2. Hocken: Schmidts Jahrbücher, 1844; cited by Parinaud.[13]

3. von Graefe, A.: True Anesthesia of the Retina, Klin. Monatsbl. Augenh., 1865; cited by Parinaud.[13]

4. Charcot, J. M.: Lectures on Diseases of the Nervous System, 1868; cited by Parinaud.[13]

5. Leber, T.: Hysterical Amblyopia, von Graefes Arch. Ophth., 1869; cited by Parinaud.[18]

6. Rosenthal: Wien. med. Presse, #23, 1879; cited by de Schweinitz.[17]

7. Moore, W. O.: Hysterical Blindness in the Male with the History of 3 Cases, Tr. Am. Ophth. Soc., p. 80, 1888.

8. Harlan, G.: Hysterical Blindness of 10 Years' Duration in a Healthy Male Subject, Tr. Am. Ophth. Soc., p. 327, 1889.

9. Babinski, J.: Hysterical Ophthalmic Migraine, Arch. neurol. **20**:305; cited by de Schweinitz.[17]

10. Pansier, P.: Ocular Manifestations of Hysteria, Paris, F. Alcan, 1892; Montpellier med. Supp., 1892, p. 439.

11. Le Danter: Color Sensitivity, Arch. med. nav. **60**:93, 1893.

12. Mitchell, J. K., and de Schweinitz, G. E.: A Further Study of Hysterical Cases and Their Fields of Vision, J. Nerv. & Ment. Dis. **19**:1, 1894.

13. Parinaud, M.: The Ocular Manifestations of Hysteria, in System of Diseases of the Eye, edited by W. T. Norris and C. A. Oliver, Philadelphia, J. B. Lippincott Company, 1900.

14. Bregmann: Ztschr. Augenh. **5**:391, 1901; cited by de Schweinitz.[17]

15. Greeff, C. R.: Berl. klin. Wchnschr., May 26, 1902; cited by de Schweinitz.[17]

16. Pfingst, A. D.: A Case of Bilateral Hysterical Amaurosis, Ophth. Rec. **14**:53, 1905.

17. de Schweinitz, G. E.: Neuroses and Psychoses, in Posey, W. C., and Spiller, W. G.: The Eye and the Nervous System, Philadelphia, J. B. Lippincott Company, 1906.

18. Prince, M.: Experiments to Determine Co-Conscious (Sub-Conscious) Ideation, J. Abnorm. Psychol. **3**:33, 1908.

19. Gross, J. H.: The Diagnostic Value of Form and Color Fields in Hysterical Amblyopia, Am. J. Ophth. **29**:193, 1912.

20. Freud, S.: Selected Papers on Hysteria, Ed. 2, translated by A. A. Brill, New York, J. Nerv. & Ment. Dis. Publ. Co., 1912.

21. Holden, W. A.: Blindness as a Wish, Psychoanalyt. Rev., November, 1913.

22. Lewis, F. P.: Psychic Disturbances Involving the Eye, Ann. Ophth. **23**:219, 1914.

23. Ames, T. H.: Analysis of Blindness as a Symptom of Hysteria, Arch. Ophth. **43**:357, 1914.

24. Parsons, J. H.: The Psychology of Traumatic Amblyopia Following the Explosion of Shells, Lancet **1**:697, 1915.

25. Campbell, K.: A Case of Hysterical Amblyopia, Brit. M. J. **2**:439, 1915.

26. Alger, E. M.: Hysterical Amblyopia, Spasm and Diplopia, Arch. Ophth. **44**:200, 1915.

27. Elder, M. D.: The Psychopathology of War Neurosis, Lancet **2**:264, 1916.

28. Hertz, A. F., and Ormond, A. W.: The Treatment of "Concussion Blindness," Lancet **1**:15, 1916.

29. Hurst, A. F., and Symns, J. L. M.: Narrow and Spiral Fields of Vision in Hysteria, Malingering, and Neurasthenia, Brit. J. Ophth. **3**:17, 1919.

30. de Schweinitz, G. E.: Concerning the Ocular Phenomena in the Psychoneuroses of Warfare, Arch. Ophth. **48**:419, 1919.

31. Duane, A.: Fuchs's Textbook of Ophthalmology, Philadelphia & London, J. B. Lippincott Company, 1919.

32. Zatler, cited by Gurvitch.[69]

33. Schwartz, cited by Gurvitch.[69]

34. Gvilo, cited by Gurvitch.[69]

35. Munzer, cited by Gurvitch.[69]

36. Freiburgh and Lacasne, cited by Gurvitch.[69]

37. Bourgh, cited by Gurvitch.[69]

38. Luck, cited by Gurvitch.[69]

39. Mandel, cited by Gurvitch.[69]

40. Rabinovitz, cited by Gurvitch.[69]

41. Eposhensky, cited by Gurvitch.[69]

42. Pfingst, A. O.: Hysteria as It Affects the Eye, Kentucky M. J. **18**:436, 1920.

43. Shastid, T. H.: Hysteropia, or the Ocular Manifestations of Hysteria, Am. J. Physiol. Optics **2**:289, 1921.

44. Garvey, J. L.: Hysterical Homonymous Hemianopsia, Am. J. Ophth. **5**:721, 1922.

45. Hartmann, H.: Ztschr. ges. neurol. u. psych'at. **74**:593, 1922.

46. Krolin, W. O.: The Psychoneuroses and Their Treatment, U. S. Nav. M. Bull. **18**:39, 1923.

47. Marin, A.: Amaurosis (Simulated or Hysterical) Due to Slight Ocular Trauma, Siglo med. **80**:73, 1927.

48. Clark, O.: Bilateral Hysterical Amaurosis, Brasil-méd. **1**:300, 1927.

49. Eszenyi, M.: Differential Diagnostic Significance of Changes of the Visual Field in Hysteria, Monatsschr. Psychiat. u. Neurol. **69-70**:147, 1928.

50. Moriez, A.: Mechanisms of Hysterical Amaurosis, Rev. oto-neuro-oftal., p. 669, 1928.

51. Rowland, W. D., and Rowe, A. W.: Marked Concentric Contraction of the Visual Fields: A Study of 100 Consecutive Cases, Tr. Am. Acad. Ophth. **34**:107, 1929.

52. Renedo, M.: Double Hysterical Amaurosis, Med. ibera **1**:311, 1929.

53. Spaeth, E. B.: Differentiation of Ocular Manifestations of Hysteria and of Ocular Malingering, Arch. Ophth. **4**:911, 1930.

54. Frey, G.: A Case of Hysterical Amblyopia, Arch. Ophth. **3**:1, 1930.

55. Peter, L. C.: The Principles and Practices of Perimetry, Philadelphia, Lea & Febiger, 1931.

56. Miranda, B.: Observation of a Case of Hysterotraumatic Blindness and Instantaneous Cure Through Faith, After a Duration of 6 Months, Bull. Soc. med.-cir. São Paulo **15**:376, 1931.

57. Feldmann, S.: A Curious Phobia, Psychoanalyt. Praxis **2**:96, 1932.

58. Guiral, R. J.: Ocular Hysteria, Med. argent. **11**:1620, 1932.

59. Ortega, J. M.: Hysterical Amaurosis Following Ocular Trauma, Rev. cubana oto-neuro-oftal. **1**:256, 1932.

60. Feldmann, S.: Psychogenic Visual Disturbances, Psychoanalyt. Praxis **3**:73, 1933.

61. Cordes, F., and Horner, W.: Hysterical Amblyopia, Am. J. Ophth. **16**:592, 1933.

62. Allen, C. N.: A Case of Hysterical Blindness from Early American History, J. Abnorm. & Social Psychol. **27**:435, 1933.

63. Charlin, C.: Simulation and Ocular Hysteria, translated by H. Coglan, Am. J. Ophth. **16**: 683, 1933.

64. Charlin, C.: Hysterical Blindness, Arch. oftal. Buenos Aires **9**:427, 1934.

65. Hamill, R. C.: Tubular Vision, Arch. Ophth. **12**:345, 1934.

66. Dupuy-Dutemps, P.: Amaurosis and Hysterical Amblyopia, Bull. Soc. opht., Paris, p. 278, 1934.

67. Ortiz, J. M. V.: Recurrent Bilateral Hysterical Amaurosis, Arch. oftal. hispano-am. **34**:381, 1934.

68. Moore, F.: Symposium on Functional Diseases of the Eye, Tr. Ophth. Soc. U. Kingdom **54**: 405, 1934.

69. Gurvitch, B. A.: Hysterical Amaurosis, Sovet. vestnik oftal. **4**:142, 1934.

70. Dupuy-Dutemps, P.: Hysterical Amaurosis: A Cure, Bull. Soc. opht., Paris, p. 6, 1935.

71. Pattie, F. A.: A Report of Attempts to Produce Uniocular Blindness by Hypnotic Suggestion, Brit. J. M. Psychol. **15**:230, 1935.

72. Lachman, G. S.: Amblyopia in Children, Tr. Pacific Coast Oto-Ophth. Soc. **21**:102, 1936.

73. Elmore, E.: Mrs. Miller: Study of Psychic Blindness, Psychoanalyt. Rev. **23**:395, 1936.

74. Renedo, M.: Terror Psychoneurosis Amaurosis, Arch. oftal. hispano-am. **36**:139, 1936.

75. Cotlier, L.: Psychic Concepts of Hysterical Amaurosis: Fundamentals in Its Psychotherapy and Prognosis, Rev. argent. neurol. **2**:211, 1936.

76. Wolff, E., and Lachman, G. S.: Hysterical Blindness in Children: Report of 2 Cases, Am. J. Dis. Child. **55**:743, 1938.

77. Bagchi, S. K.: Hysterical Manifestations in the Eye with Case Notes, Antiseptic **36**:612, 1939.

78. Hurst, A., Editor: Medical Diseases of War, Baltimore, Williams & Wilkins Company, 1940.

79. Rea, L. R.: Neuro-Ophthalmology, Ed. 2, St. Louis, C. V. Mosby Company, 1941.

80. Vandegrift, G. W.: Ocular Manifestations of Hysteria, M. Rec. **153**:3, 1941.

81. Barea, J.: Total Hysterical Recidivous Amaurosis of Both Eyes, Rev. españ. med. y c.r. guerra **4**:113, 1941.

82. King, A., and Walsh, F. B.: Temporary Amaurosis and Hemianopsia Due to Epilepsy, Am. J. Ophth. **25**:398, 1942.

83. Wolf, A.: Dynamics of the Selective Inhibition of Specific Functions in Neurosis, Psychosom. Med. **5**:27, 1943.

84. Mahoney, V. P., and Linhart, W. D.: Amblyopia in Hysteria, 13 Cases, War Med. **3**:503, 1943.

85. Davenport, R. C.: Discussion on Ocular Psychoneuroses, Tr. Ophth. Soc. U. Kingdom **64**:57, 1944.

86. Halpern, H. J.: Hysterical Amblyopia Cases, Bull. U. S. Army M. Dept. **72**:84, 1944.

87. Ruzo, G.: Hysterical Amaurosis, Rev. san mil. argent., pp. 23, Jan., 1944.

88. McAlpine, P. T.: Hysterical Defects, War Med. **5**:129, 1944.

89. Moersch, F. B.: Malingering with Reference to Its Neuropsychiatric Aspects in Civil and in Military Practice, M. Clin. North America **28**: 928, 1944.

90. Gutheil, E. A., in discussion on Lowenberg, H.: Psychomatic Relations in Function of Lachrymal Glands, J. Clin. Psychopath. **6**:473, 1944.

91. de Figueirido, N. P.: Ocular Symptoms of Hysteria, Neurobiologia **8**:129, 1945.

92. de Figueirido, N. P.: Ocular Symptoms of Hysteria, Rev. brasil. oftal. **3**:215, 1945.

93. Birge, H. L.: Ocular War Neurosis, Arch. Ophth. **33**:445, 1945.

94. Miller, R. B.: Corneal Anesthesia in Hysteria, U. S. Nav. M. Bull. **44**:749, 1945.

95. Rouquier, A.: Narrowing of Visual Field and Amblyopia of Persons with Cranial Injuries, Presse méd. **53**:71, 1945.

96. Giridhar, P. D.: Psychotherapy in Hysterical Amblyopia, Indian J. Ophth. **6**:32, 1945.

97. Yasuna, E. R.: Hysterical Amblyopia: Its Differentiation from Malingering, Am. J. Ophth. **29**:570, 1946.

98. Masserman, J. H.: Principles of Dynamic Psychiatry, Philadelphia, W. B. Saunders Company, 1946, p. 47.

99. Eames, T. H.: A Study of Tubular and Spiral Central Fields in Hysteria, Am. J. Ophth. **30**:611, 1947.

100. Redslob, E., and Brini, A.: Les méfaits de la "Symphonie pastorae," Ann. ocul. **80**:104, 1947; cited by Yasuna.[109]

101. Harrington, D. O.: Symposium: Psychosomatic Manifestations; Ophthalmology, Tr. Am. Acad. Ophth. **52**:78, 1947.

102. Kiene, H. E.: Amblyopia Due to Displacement, Rhode Island M. J. **14**:141, 1947.

103. Abt, I. A.: Hysteria in Children, M. Clin. Chicago **1**:477-487, 1915; cited by Kanner.[104]

104. Kanner, L.: Child Psychiatry, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1948, p. 550.

105. Traquair, H. M.: An Introduction to Clinical Perimetry, St. Louis, C. V. Mosby Company, 1948.

106. Wilson, J. E.: Hysterical Amblyopia, Am. J. Ophth. **31**:1635, 1948.

107. Duke-Elder, W. S.: Text-Book of Ophthalmology, Vol. IV, St. Louis, C. V. Mosby Company, 1949.

108. Garcia, J. A.: Hysterical Amaurosis and Amblyopia, Arch. Soc. oftal. hispano-am. **9**:648, 1949.

109. Yasuna, E. R.: Hysterical Amblyopia in Children and Young Adults, A. M. A. Arch. Ophth. **45**:70, 1951.

110. Gogela, L. J., and Rucker, C. W.: Psychogenic Changes in the Field of Vision Associated with Tumors of the Frontal Lobe of the Brain, Am. J. Ophth. **34**:185, 1951.

111. Feigenbaum, A.: Psychogenic Factors in Disturbances of the Visual Organ in the Light of Psychoanalysis, Acta med. orient. **12**:209, 1953.

112. Krimsky, E.: The Psychologic Approach to Children's Eye Problems, Postgrad. Med., pp. 459-462, 1954.

113. Cambiaso, R. H.: Unilateral Hysterical Amaurosis, Arch. oftal. Buenos Aires **29**:483; abstracted, Am. J. Ophth. **40**:153, 1955.

# Visual Field Defects in Exophthalmos Associated with Thyroid Disease

THOMAS R. HEDGES Jr., M.D.
and
HAROLD G. SCHEIE, M.D., Philadelphia

It is not widely recognized that exophthalmos associated with thyroid disease can be accompanied by visual loss due to involvement of the optic nerve. Loss of vision is used by many as an indication for surgical decompression of the orbit in patients with progressive exophthalmos. Through a better understanding of the factors responsible for such visual loss a more reasonable differentiation might be made between those patients who should have conservative therapy and those who should have, in addition, orbital decompression.

This report concerns six patients in whom defects could be demonstrated in central visual fields indicative of optic nerve involvement within the orbit similar to optic or retrobulbar neuritis. Three patients showed pericentral scotomas in one or both eyes, and in three patients nerve fiber bundle defects were present (Fig. 1, Cases 3, 4, and 6). Although the pathogenesis of such optic nerve defects associated with thyroid disease is unknown, both endocrine and mechanical factors have been suggested,* depending on whether emphasis is placed primarily on the relationship to thyroid dysfunction or on local ocular changes. We therefore evaluated the endocrine status and ocular manifestations in the six cases presented here in an attempt to determine what correlation, if any, exists between the severity of hyperthyroidism, the degree of exophthalmos, and the existing field defects. All of these patients had complete physical, endocrine, and ophthalmologic studies with a follow-up of 9 to 12 months. No other systemic or neurologic disease was found which would account for involvement of the optic nerve, although two of the patients had diabetes and one was in her sixth month of pregnancy. Pertinent endocrine and ophthalmologic findings at the time these patients developed visual loss and central field defects are summarized in the accompanying Table.

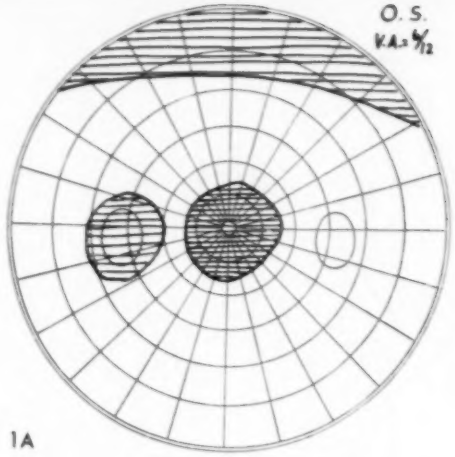
Received for publication Oct. 11, 1955.

From the Department of Ophthalmology, Hospital of the University of Pennsylvania.

* References 2 to 5.

## SUMMARY OF CASES

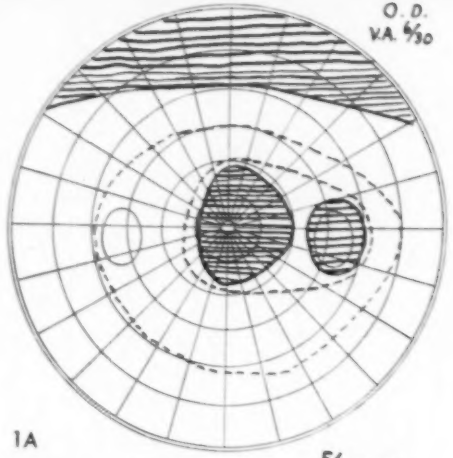
All of the patients had had hyperthyroidism at some time, but at the time the field defects occurred only two were moderately thyrotoxic, two were mildly toxic or in remission, and two were euthyroid. The two patients who had hyperthyroidism developed blurred vision and visual field defects within a few weeks after the onset of their metabolic disease. In both instances vision and fields returned to normal in approximately two months. The overactivity of the thyroid was controlled in four months in one patient and in four to five weeks in the other. Therefore, although there was a correlation between the onset of hyperthyroidism and the visual difficulty in both patients, it is debatable whether control of the thyrotoxic state had anything to do with regression in the optic nerve defects in that recovery of vision occurred prior to control of the thyrotoxic state in one patient and after control in the other. The remaining four cases were in remission or were euthy-




1A

T. F.
2-15-52

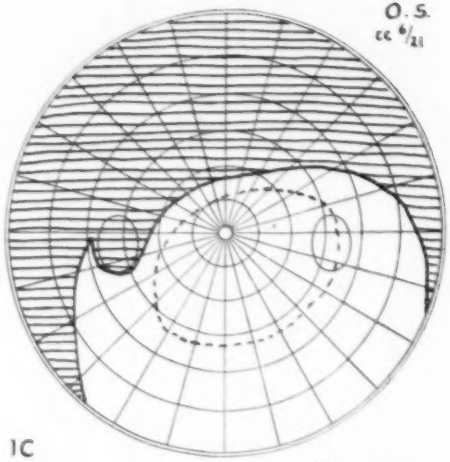
15/1000 W —




1A

T. F.
2-15-52

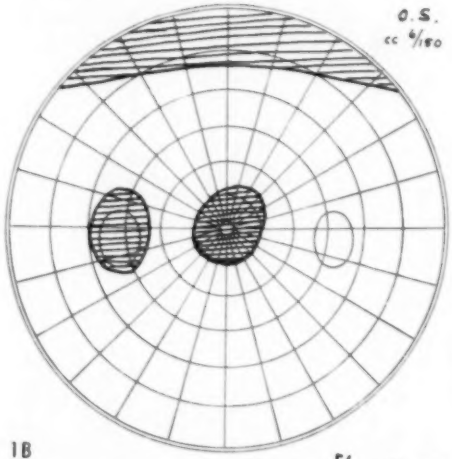
5/1000 W ---
10/1000 W —




1C

E. M.
6-30-99

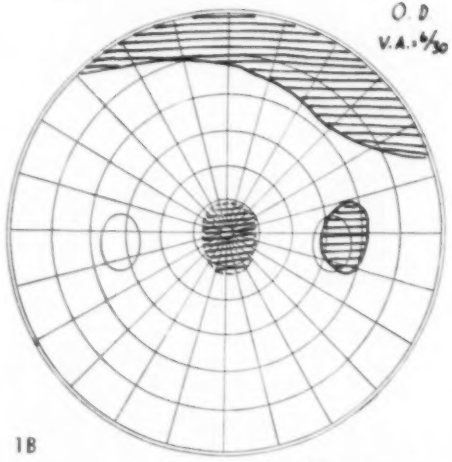
2/1000 W —
1/1000 W ---




1B

F. D.
10-28-52

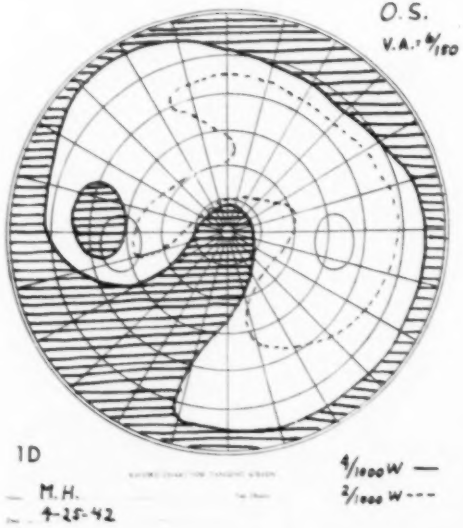
5/1000 W —

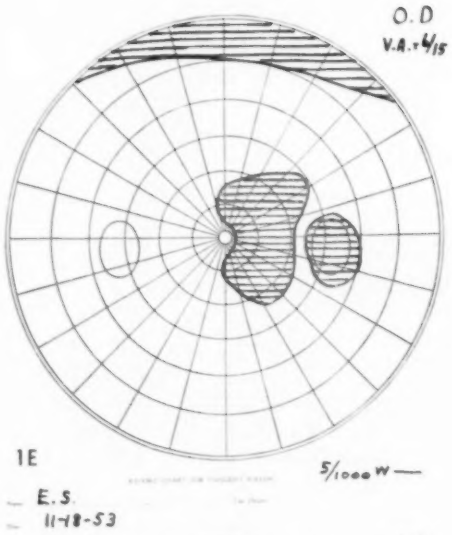


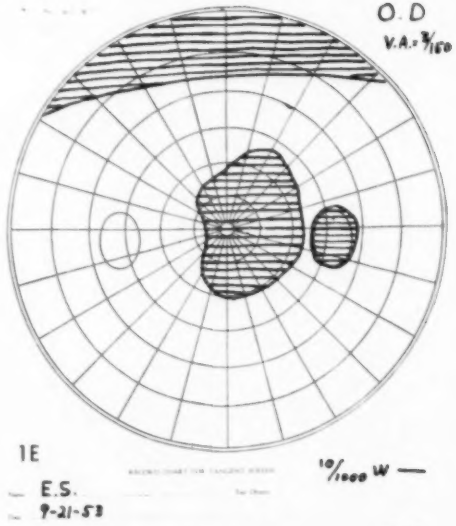

1B

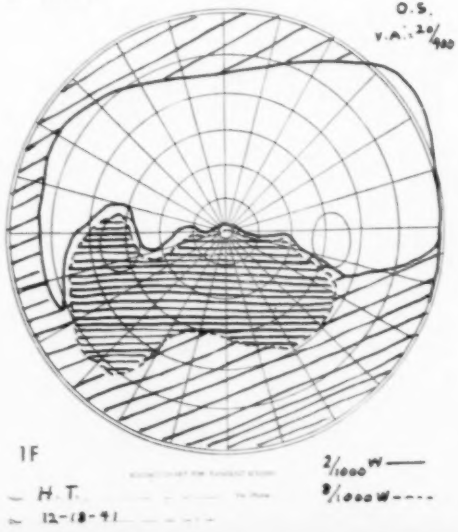
F. D.
10-23-52

5/1000 W —
2/1000 W —---



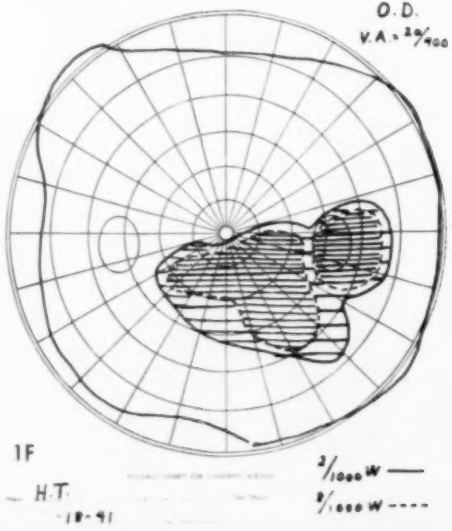




Fig. 1.—Visual charts in Cases 1, 2, 3, 4, 5, and 6

roid when the optic nerve involvement became evident. Therefore no correlation would seem to exist between thyroid dysfunction and the ocular manifestations in these patients.

The degree of exophthalmos varied greatly. In two instances (Patients 3 and 4), in which the proptosis was moderately severe and asymmetric by 3 to 4 mm., the more pronounced visual field defects and visual loss occurred in the more exophthalmic eye.

Central scotoma was present bilaterally in two patients and unilaterally in three. Three patients had nerve fiber bundle defects. The average duration of the visual loss and demonstrable field defect was approximately two months, and in all instances except one vision and fields returned to normal. In one patient (Patient 6) partial optic atrophy resulted after vision had returned from 6/150 to 6/15. This was the only patient in whom orbital decompression

*Endocrine and Ocular Data in Six Patients with Exophthalmos and Thyroid Disease*

| | | | Endocrine Status | Ocular Findings | Visual Fields | Final Result |
|---|---|---|---|---|---|---|
| 1 | F (Diabetic) | | Moderate toxicosis (+47%), related to onset of field defect | Exophthalmos, slight $\frac{18\times18}{97}$ Congestion severe (Fig. 2A) | Bilateral scotoma (central); vision reduced to 6/30 and 6/12; fundi normal | Duration: approximately 6 wk.; normal final vision and fields |
| 2 | F | 37 | Mild to moderate toxicosis, definitely related to field defect in onset (+26% to +32%) | Exophthalmos slight to moderate $\frac{22\times22}{103}$; no congestion | Amblyopia O.D. 6/30; central scotoma O.S.; vision reduced to 6/150; fundi normal | Duration: approximately 2½ mo.; normal final vision and fields O.S. |
| 3 | M | 68 | Mild toxicosis (+27%), under control; no relation to onset of field defect | Exophthalmos moderately severe and asymmetric $\frac{23\times27}{109}$; marked congestion (Fig. 2B) | Unilateral nerve fiber bundle defect in eye with most proptosis; vision reduced to 6/21; fundi normal | Duration: 3.8 wk., with normal final vision and fields |
| 4 | F | 61 | Toxicosis mild (+9%) and in remission when exophthalmos and field defect occurred | Moderate to marked congestion during course; exophthalmos moderately severe $\frac{25\times28}{105}$ | Central scotoma in one eye and nerve fiber bundle defect; vision reduced to 6/150 | Duration: 6 wk.; return of normal vision and fields |
| 5 | F (Severe diabetic) | 40 | Euthyroid; patient had palpable gland and was in remission and on thyroid extract; BMR's (3) all around 0 | Exophthalmos fairly marked with chemosis and lid edema; moderate conjunctival injection; limited EOM; Hertel $\frac{24\times30}{111}$ | Unilateral central scotoma to 10 mm. white in eye with less proptosis; became paracentral at 2 mo.; vision reduced to 3/150; minimal diabetic retinopathy | Duration: about 2.3 mo. with return to normal vision and fields |
| 6 | M | 56 | Euthyroid; previous operation, but no evidence of recurrent toxicosis; BMR's around 0 | Exophthalmos and congestion severe; retinal edema, venous engorgement, and papilledema; Hertel $\frac{28\times30}{112}$ (Fig. 2C) | Bilateral central scotoma; papilledema 3 D. O.D. and 1 D. O.S.; vision reduced to 6/150 O.U. | Duration: 6.9 mo. with optic atrophy, partial O.D. and 6/15 O.S., returned to 6/6 vision |

Two cases had less pronounced asymmetry (2 mm.), but here the more pronounced defects were on the side with less exophthalmos. Congestive phenomena were present in a moderate to marked degree in all patients except one (Patient 2), who had moderate exophthalmos and thyrotoxicosis but no congestion of the lids or conjunctiva. Although five out of the six patients did have prominent congestive signs externally (Fig. 2), only one patient showed retinal venous engorgement, retinal edema, and papilledema.

was performed, and, though no immediate postoperative improvement was found, it may well be that more serious damage was prevented by the procedure.

## COMMENT

Davis and Bastenie,[1] in 1953, reported bilateral "retrobulbar neuritis" in a patient with progressive exophthalmos associated with thyrotoxicosis. Hyperthyroidism had been present for a long period prior to the onset of the visual disturbance, and recovery was complete without resort to orbital de-

Fig. 2.—*A* (Case 1), slight exophthalmos; severe congestion; bilateral central scotoma. *B* (Case 3), exophthalmos and moderate congestion; unilateral nerve fiber bundle defect. *C* (Case 6), severe exophthalmos and congestion; bilateral central scotoma, with papillitis.

compression. They emphasized that, although optic nerve manifestations are often mentioned in the literature, these reports are not accompanied by visual fields to substantiate the diagnosis of optic or retrobulbar neuritis. From their review of the literature they collected 6 cases of papillitis and 13 cases of retrobulbar neuritis with complete visual studies and adequate follow-up. In all instances vision was markedly reduced initially. Approximately half of the patients in each group were treated with orbital decompression. The rest of the patients were managed with the usual conservative measures. There was no difference in the final results in these two groups. Of importance is the fact that of the 6 cases with papillitis, 4 had final vision of 6/15 or less, and that of the 13 patients with retrobulbar defects, 9 had normal final vision and only 2 had vision of 6/15 or less after an adequate period of follow-up. Five out of six patients in our series showed retrobulbar involvement only, and in all of these patients vision returned to normal levels within two to three months without orbital decompression. In one case only, in which papilledema was present, orbital decompression was performed and optic atrophy resulted, with final vision reduced to 6/15.

It therefore seems justifiable to conclude that prognosis for good final vision is much better when there is no intraocular involvement of the optic nerve. In addition, the outcome as regards vision per se was not affected by orbital decompression in this group of patients.

Naffziger [2] has recently summarized his experience with orbital decompression in 40 successive cases. Seventeen per cent of his patients had "visual loss associated with choked discs, but more frequently visual loss was accompanied by no discernible alterations other than a high degree of retrobulbar pressure." No mention was made of central scotomata. However, two patients had bilateral inferior altitudinal field defects. Naffziger stresses, as indications for decompression, loss of vision, progression of proptosis, and, particularly, increase in retrobulbar pressure, as determined by manometric or digital evaluation of orbital resistance. Field defects were completely restored in two out of three cases in which they were present, and in the third vision was restored and the field defect decreased. He assumed that circulatory impairment in the optic nerves accounted for these defects, since prompt restoration of vision followed when the pressure was relieved by decompression.

Two possibilities exist which might explain the optic nerve involvement in these cases of exophthalmos. The most widely accepted etiology is mechanical. However, evidence does exist that a neurotoxic pathogenesis may, at least in part, be responsible. In the presence of hyperthyroidism, when there is a definite correlation between onset and/or regression in the optic nerve defect and thyroid dysfunction, it has been postulated that a neurotoxic cause alone is responsible.† Older references are cited as stating that optic and retrobulbar neuritis are seen in the course of prolonged or excessive thyroid medication. Several authors [3] have reported instances of so-called "retrobulbar neuritis" in which central field defects developed in hyperthyroid patients who had little or no exophthalmos. Goldzieher and associates [4] recently reported two cases of retrobulbar neuritis in hyperthyroid patients. In one patient there was a definite correlation between the onset and regression of the "neuritis" and thyrotoxicosis. These authors‡ are of the opinion that the optic nerve defect was "neurotoxic" in origin. It is possible that in our first two cases thyrotoxicosis did play some part in the production of the optic nerve defect. The predominant feature in these cases was the occurrence of a central scotoma, indicative of involvement of the maculopapular bundle. Although mass lesions in the orbit can produce this type of defect by pressure on the nerve, amblyopia of this type is more commonly seen in demyelinating disease and certain neurotoxic conditions. In the absence of other signs of

† References 3 and 4.

‡ References 1 and 2.

neurologic disease, it might be inferred that this is indirect evidence in favor of a neurotoxic etiology.

When exophthalmos or congestive signs are a prominent feature, the possibility of a mechanical cause for the optic nerve symptoms seems obvious. In our cases it would appear that, with the exception of two patients in whom hyperthyroidism was present, there was a dissociation between the neurologic symptoms and thyroid dysfunction, leaving a mechanical cause as the most likely etiologic possibility.

It has been shown that in progressive exophthalmos there is an increase in volume of the retro-orbital tissues. When these changes are pronounced, it is postulated that there is an increase in orbital pressure. This is manifest externally by congestive phenomena. In four out of six cases, signs of thyrotoxicosis were not present when the field defects occurred, but all these patients had pronounced exophthalmos and signs of external congestion. In this group, therefore, mechanical factors seem most likely as the cause of the optic nerve involvement. The increase in tissue volume and rise in orbital pressure lead to circulatory impairment, which predominantly affects the maculopapular bundle.

It seems important to try to localize the site where this pressure on the optic nerve could be most pronounced. Naffziger[5] has reported cases of altitudinal defects in the visual field. Here the damage to the optic nerve was assumed to be near the optic foramen. Igersheimer has recently reported on this subject.[6] He studied six cases of progressive exophthalmos in which central scotomata were present on the visual field. Only one patient showed signs of retinal venous engorgement, and in our series only one patient showed signs of retro-orbital venous congestion, as manifested by retinal venous engorgement, retinal edema, and papilledema. If orbital pressure rises with increase in tissue volume, as is postulated in progressive exophthalmos, one would expect intraocular venous congestion to be an accompanying phenomenon. This is obviously not the case in the majority of patients in these two series, if one is to take as an indication of increased orbital venous pressure the intraocular signs just mentioned. Igersheimer states that in these cases increased orbital pressure involves the optic nerve near the optic foramen or in front of it. This hypothesis could be broadened to state that as the orbital pressure increases in progressive exophthalmos it first exerts its effect at the posterior aspect of the orbit, but that, as this pressure rises, vascular stasis is more likely to be manifest by intraocular changes. These findings would therefore be found only in the more extreme cases, where a profound increase in tissue volume in the orbit is present. Another explanation for the lack of intraocular signs of venous obstruction is the large venous anastomosis between the orbital and the facial veins, through which any increased venous pressure in the orbit is readily dissipated. These factors could explain the wide variation in clinical signs in our patients and the relative absence of congestive intraocular signs.

Recently Day and Werner[7] described radioactive sodium studies on the orbit. They concluded:

> Venous obstruction is not the factor responsible for the edema and proptosis associated with the ophthalmopathies of thyroid disease, particularly the severe form. Instead, an active inflammation with arterio'ar dilatation and increased permeability is suggested as the responsible mechanism.

We do not take issue with this statement, but merely wish to point out that in the discussion above venous stasis was referred to only as a secondary effect, from increased tissue volume, and it is not inferred that it has anything to do with initial tissue changes present in the hyperophthalmopathic syndrome.

## SUMMARY

We have reported six cases of exophthalmos associated with thyroid disease which had central visual field defects and reduced vision. In the absence of any other recognizable ocular defect, it must be assumed that this condition is due to involvement of the optic nerve in the orbit.

No direct relationship existed between thyroid activity and the optic nerve involvement in the majority of these patients. Visual loss was more pronounced in the more exophthalmic eye only when asymmetry of proptosis was marked (3 to 4 mm.).

Two schools of thought exist as to the pathogenesis of this phenomenon. A neurotoxic mechanism is possible when thyrotoxicosis is related to the onset or remission of optic nerve defects, and preferably when marked exophthalmos is not present. However, mechanical factors are of primary importance in most instances. Increased tissue volume in the orbit and subsequent rise in orbital pressure lead to pressure on the nerve and impairment of its circulation. The field defects described in this paper are characteristic of such a process affecting the optic nerve.

The prognosis in those cases with retrobulbar involvement of the optic nerve is good in that the majority show return to normal vision and fields within a few months. In those cases in which papilledema is present over a prolonged period of time, the visual prognosis is considerably worse because of the danger of secondary optic atrophy. Surgical decompression of the orbit is most justified in this latter group of patients and can be avoided in those patients who have visual loss due to retrobulbar involvement of the nerve, unless accompanied by severe external signs and corneal defects.

## REFERENCES

1. Danis, P., and Bastenie, P.: Diseases of the Optic Nerve in the Course of Endocrine Edematous Exophthalmos, Ophthalmologica **126**:65-90, 1953.

2. Naffziger, H. C.: Progressive Exophthalmos, Bull. Am. Coll. Surgeons **40**:33-39 and 53-55, 1955.

3. Brown, R. B., and Schwarz, G. A.: Optic Neuritis in Hyperthyroidism: Report of Case with Review of the Literature, Arch. Int. Med. **60**:668-679, 1937.

4. Goldzieher, M. A., and others: Retrobulbar Neuritis Associated with Hyperthyroidism, A. M. A. Arch. Neurol. & Psychiat. **65**:189-196, 1951.

5. Naffziger, H. C.: Pathologic Changes in Orbit in Progressive Exophthalmos, with Special Reference to Alterations in Extra-Ocular Muscles and Optic Disks, Arch. Ophth. **9**:1-12, 1933.

6. Igersheimer, J.: Visual Changes in Progressive Exophthalmos, A. M. A. Arch. Ophth. **53**:94-104, 1955.

7. Day, R. McC., and Werner, S. C.: Removal Rate of Radiosodium ($Na^{24}$) from Human Orbit in Graves' Disease and in Health, A. M. A. Arch. Ophth. **52**:85-90, 1954.

# Unequal Corrected Visual Acuity as Related to Anisometropia

ARTHUR JAMPOLSKY, M.D.
BERNICE C. FLOM, O.D.
FRANK W. WEYMOUTH, Ph.D.
and
LINCOLN E. MOSES, Ph.D., San Francisco

It is well known that corrected acuity in ametropia is usually normal, or approximately so, but is sometimes markedly reduced. In many cases this low acuity occurs in eyes which appear normal, even to careful examination. Often the corrected acuity differs markedly in the two eyes; for example, one may be 20/15 and the other 20/40. In some cases unequal acuity is known to be associated with unequal refraction or anisometropia. Anisometropia, it is generally agreed, presents difficult problems of correction. Many writers have speculated regarding the possible relations of corrected acuity to refractive conditions, but satisfactory statistical analyses are lacking. The clinical importance of the problems, particularly in the correction of anisometropia in children, justifies a reexamination of the question with material selected to present those refractive conditions mentioned. The present study is an attempt to apply adequate statistical analysis to appropriate data.

## SOURCE OF DATA AND TERMINOLOGY

The material of the present study consists of approximately 200 private patients meeting the following requirements: *(a)* 1.00 D. or more of anisometropia or at least 1.00 D. of astigmia in one eye; *(b)* ametropia of not more than +7.00 D. in any meridian; *(c)* absence of strabismus; *(d)* no observable pathology of the media or fundi; *(e)* age less than 55 years, to avoid minimal pathological changes.

All patients were examined by the same person (A. J.), using Green's refractor and a transilluminated Snellen visual acuity chart. The data recorded for each eye of each subject were the best subjectively determined correction and the monocular visual acuity with the correction in place. The correction was written with the cylinder positive.

We have used the term anisometropia to indicate any difference in refraction between the two eyes. Oxyopia is here used for the inherent acuity capacity of the retinocortical apparatus, hence synonymous with corrected acuity; iso-oxyopia indicates equal corrected acuity of the two eyes; aniso-oxyopia, unequal acuity. In place of amblyopia, we have preferred aniso-oxyopia as being without implications regarding possible origin, or response to training, of the difference in corrected acuity concerning which these data furnish no information. Since the term amblyopia, in spite of its implications, is commonly applied to acuities falling below some arbitrary limit, many of the cases studied would be called "amblyopia."

## TREATMENT OF DATA

The acuity scale here used for statistical analysis is the Snellen fraction multiplied by 50[1]; thus, 20/20=50, 20/40=25, etc. This scale was chosen because it gave for the distributions of differences the most nearly normal distribution; that is to say, it is a statistical convenience and carries no further implications.

Of the possible refractive values, four were used in the analysis. The equivalent sphere, calculated in the usual manner as the average of the highest and the lowest meridians, although it ignores astigmia, has proved useful for certain purposes. The three factors, the ametropia difference in the horizontal meridian, the ametropia difference in the vertical meridian, and the astigmia difference, were chosen for regression analysis. These correspond to the values of the prescription in the two

Received for publication Oct. 10, 1955.

The investigative work described in this paper was aided by a grant from the National Society for the Prevention of Blindness.

From the Division of Ophthalmology, Department of Surgery, Stanford University School of Medicine (Jampolsky and Flom). Professor Emeritus, Department of Physiology, Stanford University, and Los Angeles College of Optometry (Weymouth). Associate Professor of Statistics, Stanford University School of Medicine (Moses).

meridians and to the value of the cylinder. The axes of the cylinders, as is usually the case, were nearly all in the horizontal or vertical meridians. In the few cases of oblique astigmia values were calculated for the horizontal and the vertical. The differences in acuity were plotted as functions of three refractive differences (Figs. 1 to 6), and these differences were used in regression calculations.

In order that the sign of a regression coefficient might have a similar interpretation in each of the three groups, and for each of the three refractive differences, the differences were constructed in the following way: The cylinder was always written as positive, so that a positive value of the difference R. E.—L. E. denotes greater astigmia in the right eye. The differences in vertical and horizontal ametropia were also constructed so that a positive value of the difference R. E.—L. E. would denote greater ametropia (in the particular meridian) for the right eye. The rule used is as follows: The size of the difference is the same as the size of the algebraic difference R. E.—L. E., and the sign of the difference is taken as positive if the right eye is the more ametropic. The following examples (ametropia in the vertical meridian) illustrate the application of this rule*:

| | R. E. | L. E. | Difference |
|---|---|---|---|
| Hyperopia | +4.00 | +1.00 | +3.00 |
| Myopia | −4.00 | −1.00 | +3.00 |
| Mixed astigmia | −4.00 | +1.00 | +5.00 |

## STATISTICAL ANALYSIS

Because of the number of variables requiring consideration, statistical treatment of the relation of the acuity of an eye both to its fellow and to all the aspects of refraction of the two eyes is complex and tedious. In consequence, few attempts have been made, and these are inadequate.

In this discussion the details of standard statistical methods have been omitted. All statements apply only to the sample under consideration, which, it should be emphasized, is highly selected and does not represent either the general population or private practice. Only by selection could enough cases of anisometropia be obtained to permit the analysis here attempted.

*Individual Eyes.*—Analysis may be made with the individual eye as the unit (disregarding its relation to the fellow eye) or with the eye pair as the unit. The former is statistically simpler and has, therefore, been the attack usually followed, but it ignores the relations implied by all terms beginning with iso- or aniso-, which, as we have seen, are at the center of the problem.

As may be seen from Table 1, the numbers of men and women are very nearly equal, but the number of myopic eyes is nearly double that of hyperopic eyes. In the general population hyperopia is commoner, particularly among young people, and myopia is slightly commoner, especially the higher degrees, among women. The data give no indication of an association between sex and

* This method of coding the data will, upon reflection, be seen as unexceptionable for myopes and hyperopes; in the case of mixed astigmia difficulties may arise. For example, if the vertical ametropia in the two eyes were R. E. +2.00 and L. E. −2.00, the case would have to be excluded, since neither eye is more ametropic in the vertical meridian. (Three such cases were excluded.) Perhaps just as bad is the fact that if in one eye the reading be changed by a half-diopter, then the difference given by the rule depends very strongly on which eye is increased. Thus:

| R. E. | L. E. | | Difference |
|---|---|---|---|
| +2.00 | −2.00 | | 4.00 |
| +2.50 | −2.00 | | +4.50 |
| +2.00 | −2.00 | (+cr−) | 4.00 |

Despite the unsatisfactory feeling this gives, the method described was applied in mixed astigmia, as well as in myopia and hyperopia. If the method of measurement is indeed inappropriate, then it may be expected to mask relationships between acuity and refractive error, but not to generate fictitious relations.

The use of differences is well suited to show the relations between the eyes of a pair, but does not display the absolute degree of ametropia in either eye. Thus, the following two pairs of refractions are treated identically in terms of differences:

(*a*) R. E.: +1.00 sph ⊂ +3.00 cyl, ax 90 L. E.: +1.00 sph ⊂ +3.00 cyl, ax 180

(*b*) R. E.: +4.00 sph ⊂ +3.00 cyl, ax 90 L. E.: +4.00 sph ⊂ +3.00 cyl, ax 180

On the other hand, the method of equivalent spheres indicates the absolute degree of ametropia but ignores astigmia, presenting both vertical and horizontal meridians as equal. Thus, in (*a*) above the spherical equivalent for each eye is +2.50, although the two meridians differ by 3.00 D.

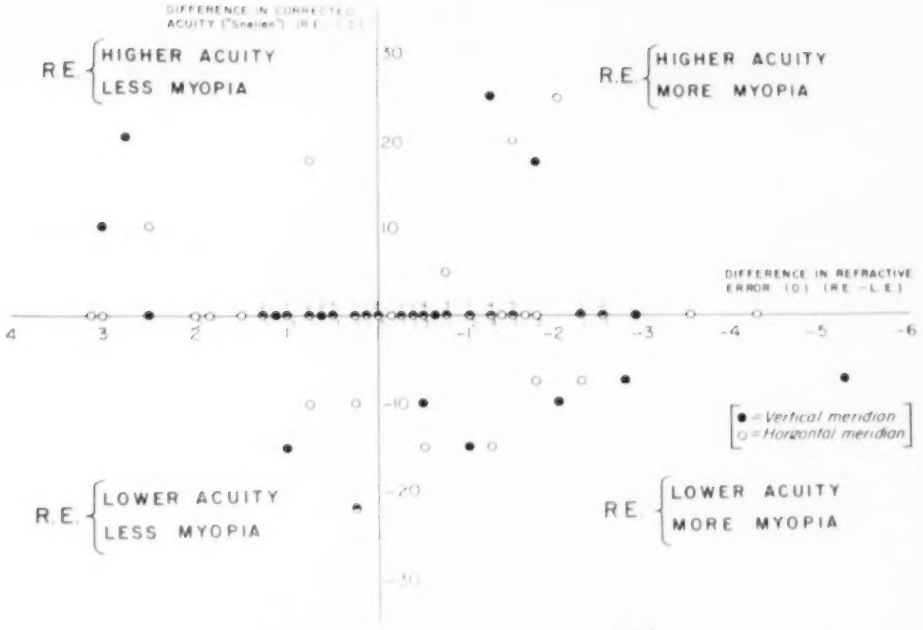

DIFFERENCE IN CORRECTED ACUITY ("Snellen") (R.E. − L.E.)
R.E. HIGHER ACUITY LESS MYOPIA
R.E. HIGHER ACUITY MORE MYOPIA
R.E. LOWER ACUITY LESS MYOPIA
R.E. LOWER ACUITY MORE MYOPIA
50
20
10
-10
-20
-50
DIFFERENCE IN REFRACTIVE ERROR (D) (R.E. − L.E.)
4 3 2 1 -1 -2 -3 -4 -5 -6
● = Vertical meridian
○ = Horizontal meridian
MYOPES (N = 105)

Fig. 1.—Scatter plot showing the relationship between differences in corrected visual acuity and differences in ametropia for the myopes. The "Snellen" acuity is the "50 times Snellen fraction" notation.

type of refraction; the $\chi^2$ test yields a probability of 0.50.

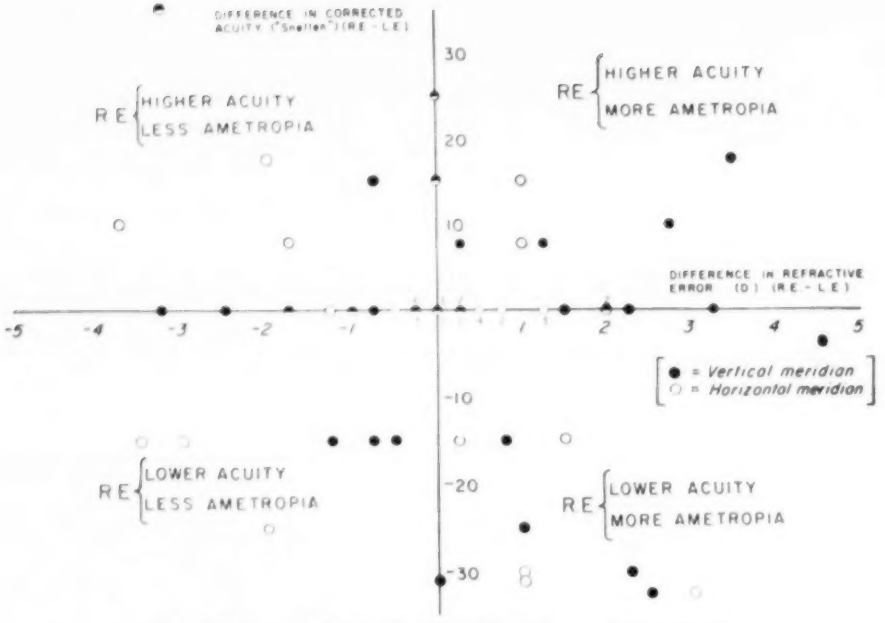
The problem of a satisfactory scale for the statistical treatment of acuity was considered, and a scale of 50 times the Snellen fraction was adopted, since certain distributions of differences appeared normal when plotted in this form. Fractions are also avoided by this method. It is not considered a solution of the difficult problem of the "best" scale for acuity.

If there were a tendency for acuities to fall into two groups, normal and amblyopic, some bimodality or discontinuity should appear in the frequency distribution. The distribution of all acuities is an extreme "J type," with the mode at the highest acuity (20/15) and the frequencies falling rapidly for lower values. The frequencies fall regularly from the mode to a vanishing point, with no significant peaks or discontinuities indicative of a separation between a "normal" and an "amblyopic" group of eyes.

TABLE 1.—*Classification of Subjects by Sex and Ametropia*

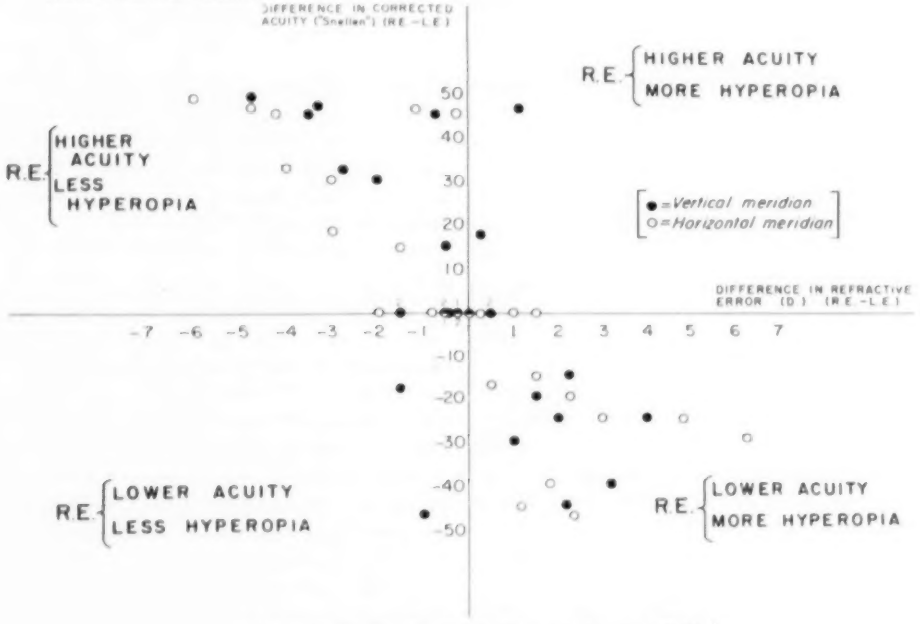
| | Men | Women | Total |
|---|---|---|---|
| Myopia | 70 | 67 | 137 |
| Hyperopia | 32 | 38 | 70 |
| Total | 102 | 105 | 207 |

*Eye Pairs.*—There is a high correlation between the corresponding parts of the two eyes of a pair. This is true not only of the dimensions of the globe (Weymouth and Hirsch[2]) but of the refractive state. Thus, the condition of isometropia is so common that the word is seldom used, whereas the absence of equal refraction is noteworthy and the word anisometropia is well known. In the same way, equal acuity, or iso-oxyopia, is the rule, as contrasted with aniso-oxyopia. These facts underline the importance of considering the relations between the eyes of a nonstrabismic pair. This complex statistical problem was attacked in two ways, both useful but neither wholly satisfactory. As



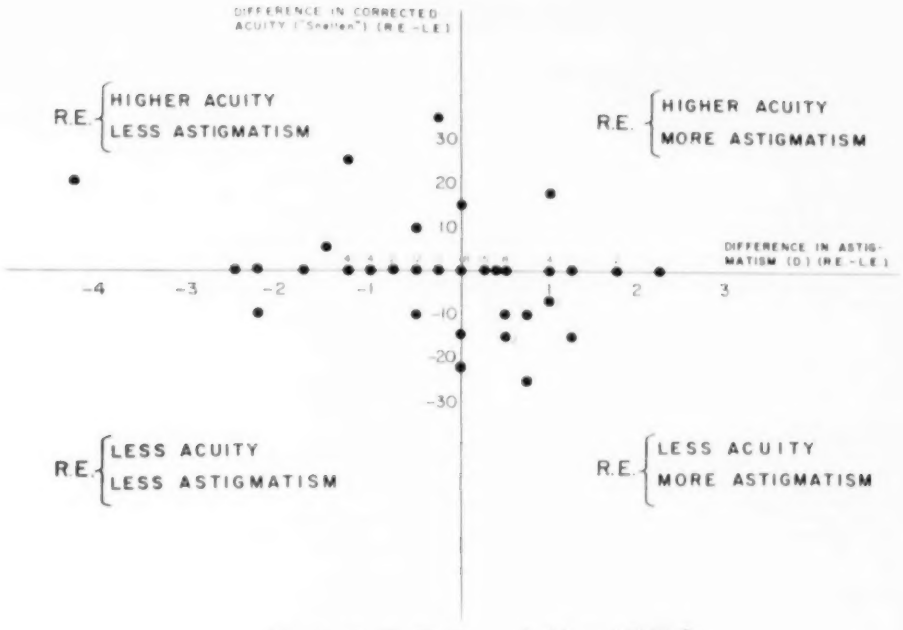

MIXED ASTIGMOPES (N = 37)

Fig. 2.—Scatter plot showing the relationship between differences in corrected visual acuity and differences in ametropia for the mixed astigmopes. The "Snellen" acuity is the "50 times Snellen fraction" notation.



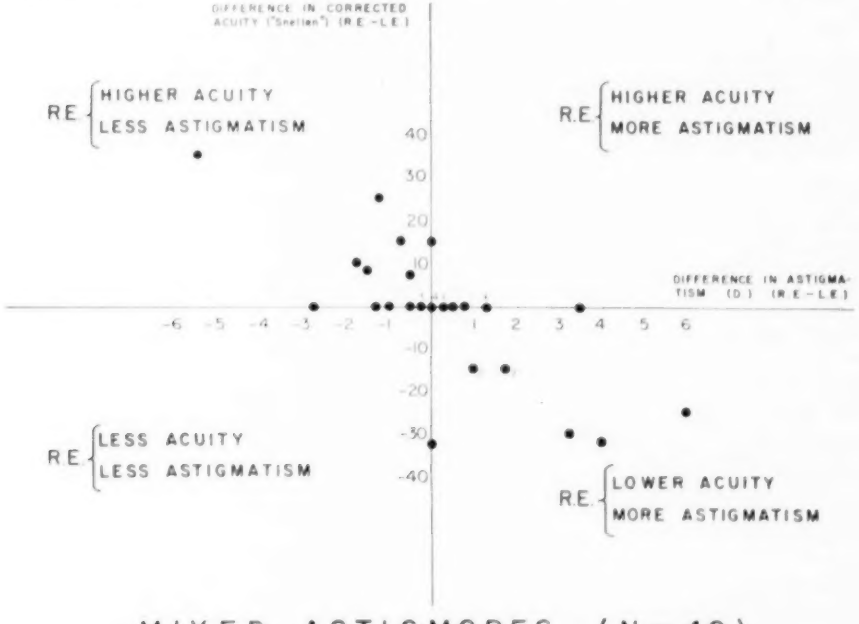

HYPEROPES (N = 60)

Fig. 3.—Scatter plot showing the relationship between differences in corrected visual acuity and differences in ametropia for the hyperopes. The "Snellen" acuity is the "50 times Snellen fraction" notation.




MYOPES (N = 105)

Fig. 4.—Scatter plot showing the relationship between differences in corrected visual acuity and differences in astigmia for the myopes. The "Snellen" acuity is the "50 times Snellen fraction" notation.




MIXED ASTIGMOPES (N = 40)

Fig. 5.—Scatter plot showing the relationship between differences in corrected visual acuity and differences in astigmia for the mixed astigmopes. The "Snellen" acuity is the "50 times Snellen fraction" notation.

1947

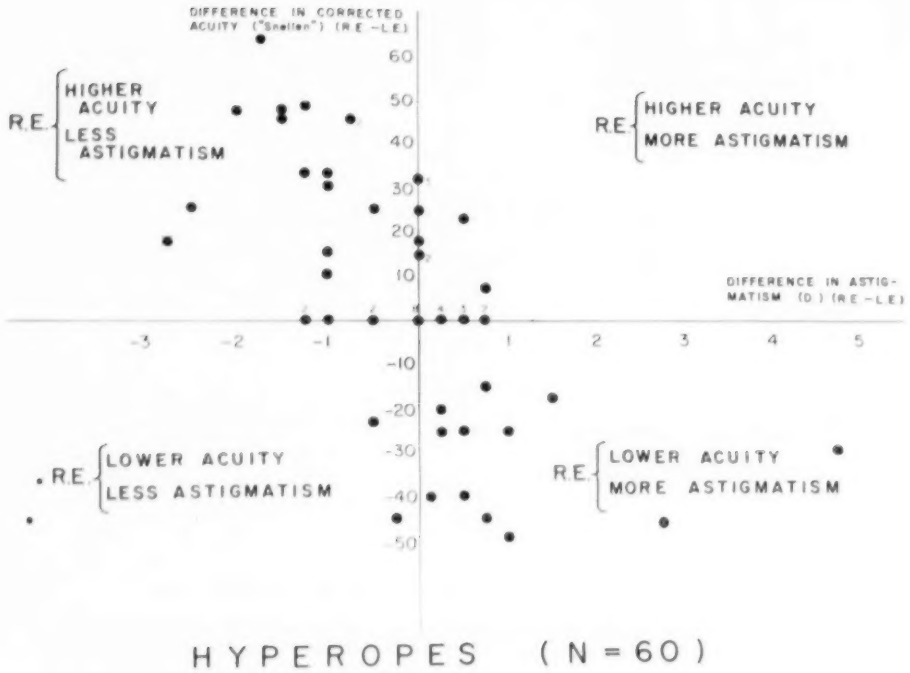

DIFFERENCE IN CORRECTED ACUITY ("Snellen") (R.E.–L.E.)
R.E. HIGHER ACUITY LESS ASTIGMATISM
R.E. HIGHER ACUITY MORE ASTIGMATISM
DIFFERENCE IN ASTIGMATISM (D.) (R.E.–L.E.)
R.E. LOWER ACUITY LESS ASTIGMATISM
R.E. LOWER ACUITY MORE ASTIGMATISM
HYPEROPES (N = 60)

Fig. 6.—Scatter plot showing the relationship between differences in corrected visual acuity and differences in astigmia for the hyperopes. The "Snellen" acuity is the "50 times Snellen fraction" notation.

Table 2.—*Classification of Subjects by Kind of Ametropia and Presence or Absence of Anisometropia*

| | Myopia | Hyperopia | Total |
|---|---|---|---|
| Isometropia | 54 | 23 | 77 |
| Anisometropia | 85 | 47 | 132 |
| Total | 139 | 70 | 209 |

already explained, the initial classification was made, first, by equivalent spheres and, second, on the basis of differences.

For the first method, in which classification is made on the basis of equivalent spheres into myopia and hyperopia, and also into isometropia and anisometropia, the data are shown in Table 2. There is no evidence of association between the type of ametropia and the presence or absence of equal refraction in the pair. (The $\chi^2$ test gives a probability of 0.40.) The same relation will be shown by other analyses, to be presented later. The high proportion of anisometropia, far above that in the general population, is, of course, due to the selection of material. It should be noted that the astigmia has been averaged out by the method of equivalent spheres (in the data of Table 2), but analysis in terms of differences, which does take account of differences in astigmia, also leads to the conclusion that the relative frequency of isometropia is not different between the myopic and the hyperopic samples.

When the classification is made by refraction and by acuity, the resulting tabulation

Table 3.—*Classification of Subjects by Kind of Ametropia and Presence or Absence of Aniso-Oxyopia*

| | Myopia | Hyperopia | Total |
|---|---|---|---|
| Iso-oxyopia | 102 (83.1) | 23 (41.9) | 125 |
| Aniso-oxyopia | 37 (55.9) | 47 (28.1) | 84 |
| Total | 139 | 70 | 209 |

(Table 3) shows a different relation. In most cases of iso-oxyopia the vision of the pair was 20/15 or 20/20, whereas the lower acuity in aniso-oxyopia fell in some cases to less than 20/400. Enclosed in brackets are the numbers to be expected if there were no association between the variables of classification. It will be seen that in myopia there is a relative excess of cases of iso-oxyopia (in terms of equivalent spheres), and in hyperopia, a relative deficiency.

Tables 2 and 3 indicate that, although the samples of myopic and hyperopic eyes do not differ with regard to the relative frequency of isometropia, they do differ with regard to the relative frequency of iso-oxyopia. Further, the distribution of acuity is markedly different in the hyperopic and myopic samples, as can be seen from Table 4. The general tendency toward lower acuity in the hyperopic sample is statistically significant at the 5% level by the Wilcoxon test, which uses only the ranks of the values of the observations, and thus will yield the same conclusion regardless of what scale is chosen for measuring acuity.

If the cases are sorted into degrees of ametropia on the basis of equivalent spheres, and also into "better" (nearer emmetropia) and "worse" eyes, and the average acuity is calculated for each of the resulting groups, the results shown in Figure 7 are obtained. This method has obvious shortcomings, since, by ignoring astigmia, it gives too simple a classification of ametropia. Nonetheless, it brings out certain points of practical importance hitherto overlooked and not easily shown by other methods.

TABLE 4.—*Frequency Distributions of Acuity*

| Denominator Snellen Fraction | Fifty Times Snellen Fraction | Myopia | Hyperopia |
|---|---|---|---|
| 1000 | 1.0 | 0 | 1 |
| 667 | 1.5 | 0 | 1 |
| 400 | 2.5 | 0 | 1 |
| 200 | 5.0 | 1 | 2 |
| 100 | 10.0 | 0 | 6 |
| 70 | 14.3 | 1 | 6 |
| 50 | 20.0 | 2 | 4 |
| 40 | 25.0 | 12 | 12 |
| 30 | 33.3 | 7 | 8 |
| 25 | 40.0 | 23 | 12 |
| 20 | 50.0 | 47 | 36 |
| 15 | 66.7 | 117 | 29 |
| 10 | 100.0 | 0 | 2 |
| Totals | | 210 | 120 |

TABLE 5.—*Summary of Test Statistics and Probability Levels*

| | Variance-Ratio Test | Wilcoxon Test |
|---|---|---|
| Differences in power of cylinder | | |
| Hyperopia not different from myopia | $F=1.19$; $P>0.05$ | $t=1.41$; $P=0.15$ |
| Differences in acuity | | |
| Hyperopia more variable | $F=12.08$; $P<0.001$ | $t=10.18$; $P<0.001$ |

If the line representing the average acuity of the better eye is considered, it will be seen that for a short range, including emmetropia, the acuity is almost 20/15, but declines with increase of myopia, and slightly more rapidly for an increase of hyperopia. For the range of ametropia covered by the sample, average acuity does not fall below 20/20. For the worse eye there is apparent at once a greater difference between myopia and hyperopia. As might have been expected from the fact that equality of acuity is commoner in myopia, the average acuity of the worse eye in myopia falls but little below its better fellow. For the worse eye in hyperopia, however, the fall in acuity is more rapid with increase of ametropia, so that at 4.00 or 5.00 D. the average is about 20/40, as contrasted with 20/20 for the better eye. This throws light on findings such as those of Broekema,[3] who found that the average acuity of hyperopic eyes is below that of myopic eyes. In the present material the average of all hyperopic eyes would fall below that of all myopic eyes, not because low corrected acuity is characteristic of hyperopic eyes but because of the aniso-oxyopia and the consequent low acuity of the "worse" eye in some of the hyperopic pairs.

The second method of study makes use of the differences in ametropia and in acuity within the pair. Three differences in ametropia were used: between the horizontal meridians, between the vertical meridians,

and between the two cylinders representing the astigmia. The difference in acuity may then be plotted as a function of each of three refractive differences. These data, so plotted, are given for the myopes in Figures 1 and 4 and for the hyperopes in Figures 3 and 6.

Before the regression of acuity on the three refractive factors is considered, certain general features deserve notice. If the distributions of the differences in astigmia and myopic samples do not differ in degree of anisometropia, there is a large and statistically significant contrast in acuity differences, hyperopia being associated with a greater variability and, in general, a higher degree of aniso-oxyopia.

The multiple regression of acuity difference (R. E.—L. E.) on differences in astigmatism, in vertical ametropia, and in horizontal ametropia (all differences of the form R. E.—L. E.), was calculated for the hy-

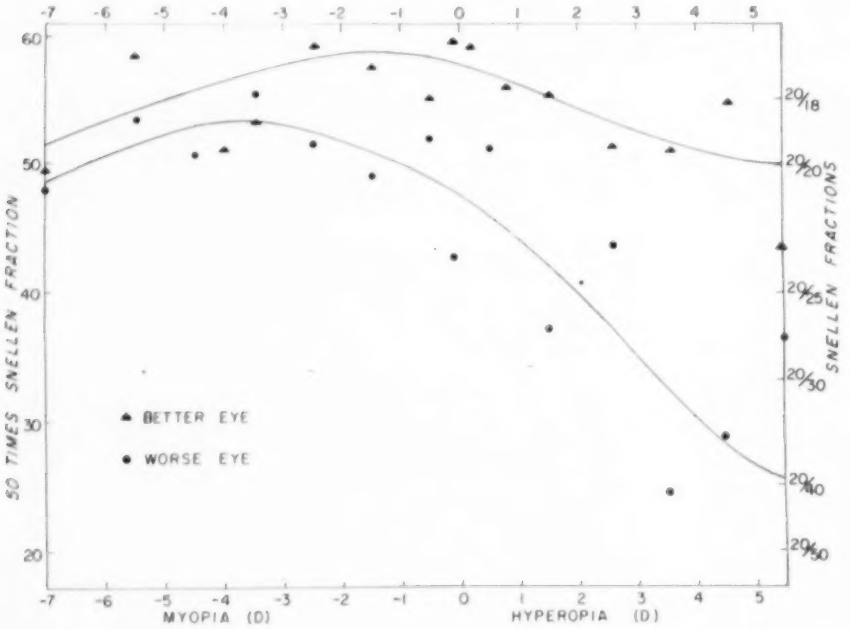



Fig. 7.—Graph of the corrected visual acuity as a function of the degree of ametropia (spherical equivalents).

in acuity are compared, it will be seen that, while the differences in the cylinders are about the same for myopia and hyperopia, the differences in acuity are much more variable and reach larger values for hyperopia than for myopia. These differences between the refractive states are significant either by the variance-ratio method, which uses the scales, or by the Wilcoxon test, which deals only with ranks.

This is in agreement with the findings above that, whereas the hyperopic and peropes and for the myopes. The regression coefficients and their standard errors are displayed in Table 6. It should be noted that the negative sign means that the eye with greater correction tends to be the eye with less acuity.

The degree of aniso-oxyopia is very strongly related to the degree of refractive difference in the sample of hyperopes. This is attested to by the large value (0.708) of $R^2$ (Table 8), and can also be sensed from inspecting Figures 3 and 6, where there is

TABLE 6.—*Regression Coefficients*

| Regression of Corrected Visual Acuity Difference on: | Regression Coefficients and Standard Deviations | | |
|---|---|---|---|
| | Myopia | Mixed Astigmia | Hyperopia |
| Astigmia difference | +.167±0.020 | 4.000±0.700 | −7.10±2.877 |
| Vertical ametropia difference | −0.060±0.030 | 0.853±1.060 | −5.15±2.245 |
| Horizontal ametropia difference | −0.456±0.030 | 0.481±1.077 | 3.59±2.338 |

a strong diagonal concentration of points. Similar inspection of Figures 1 and 4 suggests a much weaker dependence of the degree of aniso-oxyopia upon refractive difference in the myopic sample. The lower, but still significant, value of $R^2$ (0.131) attests to the weaker association in the case of myopes only. The regression on differences in astigmia is statistically significant in all types of ametropia. In the case of the hyperopes the regression coefficient for the vertical meridian is statistically significant.

A consideration of the regression of differences in corrected acuity between the two eyes on differences in three selected measures of ametropia permits the following statements which pertain to the present sample:

(*a*) Unequal acuity is significantly associated with differences of ametropia, the eye having the higher degree of ametropia showing the lower acuity.

(*b*) The difference in the horizontal meridian, the difference in the vertical meridian, and the difference in the amount of astigmia, in that order, show an increasing degree of association with acuity.

(*c*) Myopia, mixed astigmia, and hyperopia, in that order, show an increasing degree of association with acuity.

(*d*) The greatest degree of unequal acuity thus occurred in cases with the greatest difference in hyperopic astigmia, and the least degree of unequal acuity occurred in cases with low anisometropia in the horizontal meridian of myopes.

TABLE 7.—*Probabilities for Corresponding Regression Coefficients*

| | Myopia | Mixed Astigmia | Hyperopia |
|---|---|---|---|
| Astigmia difference | 0.02* | 0.001* | 0.02* |
| Vertical ametropia difference | 0.40 | 0.45 | 0.05 |
| Horizontal ametropia difference | 0.50 | 0.65 | 0.20 |

* Underlined values considered significant.

TABLE 8.—*Multiple Regression Coefficients*

| | Myopia | Mixed Astigmia | Hyperopia |
|---|---|---|---|
| $R^2$ | 0.131 | 0.567 | 0.708 |
| $R$ | 0.362 | 0.754 | 0.841 |

All values significant at the 0.1% level.

## COMMENT

Although the present study does not offer proof of the manner in which unequal corrected acuity arises, it throws into relief several aspects that deserve attention and suggests the direction that future study should take.

The strikingly high incidence of aniso-oxyopia in hyperopes as compared with myopes is the outstanding fact. It suggests that under average conditions in children, few of whom have adequate correction and wear glasses from an early age, the two eyes of myopes usually develop normally, whereas in many hyperopes the full development of acuity fails in one eye. The degree of aniso-oxyopia is associated with anisometropia, particularly with differences in astigmia. These associations are present in both myopes and hyperopes, but the association is closer, and the number of cases and the degree of aniso-oxyopia are greater, in hyperopia. While it is notorious that correlation or association describes conditions and does not prove causes, it is difficult to escape the implication of cause in the present case. We shall return to this point.

The implication of a critical period in childhood affecting the development of acuity here noted receives strong support from a study by Juler [4] of vision following operation for unilateral traumatic cataract occur-

ring at early known ages in children. Examination made several years after successful operation showed that no child who was below the age of 6½ years at the time the opacity developed had obtained a visual acuity of more than 6/36, whereas all children above this age reached 6/12 or better.

It has been suggested that the factor retarding the development of acuity is the absence of clear images during the critical period, before 6 years of age. This agrees with the views of Chavasse and others. How would such a suggestion apply to the present material? The blurred images of out-of-focus refractive apparatus produce equal accommodation in the two eyes. What amount of accommodation may be expected? Here there is a marked difference between anisomyopia and anisohyperopia. In myopia there will be objects at such distances as to be clear to one eye or the other. There is no reason that one of the eyes should always be deprived of clear images. The uncorrected anisohyperope faces a different problem. No object at any distance will be clear without some degree of accommodation. It seems probable that the unfocused images will evoke only that amount of accommodation necessary to clear the image in the less hyperopic eye, while the more hyperopic eye will never enjoy good images. In the present data it is the more hyperopic ("worse") eye that shows the lower acuity in unequal corrected acuity.

In uncorrected anisometropia without strabismus, there is a tendency to use for fixation that eye giving the clearer image or in which the image may more easily be cleared by accommodation. The fellow eye has to put up with an amount of blurring of its retinal images determined by its refractive difference from the dominant eye, to which the accommodation is adjusted. A similar mechanism has been proposed by Copps.[5]

Although the hypothesis of the accommodative origin of unequal corrected acuity is appealing, alternative or supplemental possibilities exist, of which some may be mentioned. As is well known, the correction of anisometropia with ordinary lenses, insofar as the ametropia is refractive, and this includes all astigmia, will produce differences of image size between the two eyes. Such aniseikonia, in nonstrabismic patients, may lead to suppression. To what extent suppression due to aniseikonia or to persistent dominance of the eye with the better image may have played a part in producing the aniso-oxyopia of the present material is not known, since routine tests for these conditions were not made.

For the present group of anisometropic nonstrabismic patients the possibility therefore exists that the unequal corrected acuity observed had a mixed origin, since it is impossible to evaluate the part played by several proposed mechanisms of origin, viz., absence of correction in early childhood, the accommodative posture in anisometropia, the suppression or related phenomena, and the optical effects of the spectacle lenses.

*Clinical Implications.*—If aniso-oxyopia appears to develop in childhood and to be associated with the absence of clear images at an early stage in the development of acuity, then, in order to combat aniso-oxyopia, it would seem desirable to provide early and adequate refractive correction for anisometropic hyperopia, particularly that involving astigmia.

Obviously, many factors must be taken into account in dealing with the vision of children. Early optical correction in children is not always practical, and one must bear in mind the occasionally contrasted goals of visual comfort and iso-oxyopia. Furthermore, in view of the high incidence of unequal corrected acuity in hyperopes as compared with myopes, it would seem well to shift some of the customary concern from myopes to hyperopes.

## SUMMARY

A sample of approximately 200 patients from private practice, selected as showing no apparent pathology, no opacities of the media (no person was over 55 years of age), and no strabismus, but all with anisome-

tropia of at least 1.00 D. or astigmia of 1.00 D. in one eye, were studied statistically. Particular attention was given to the relation of corrected visual acuity to certain refractive differences between the eyes of the pair. The following are the essential findings:

1. When the cases are sorted on the basis of equivalent spheres, there is a striking difference between myopia and hyperopia in the relation of the corrected acuities of an eye pair.

(*a*) Equal corrected acuity (iso-oxyopia) is significantly commoner in myopia than in hyperopia.

(*b*) Unequal corrected acuities (aniso-oxyopia) are both significantly commoner and reach higher values in hyperopia than in myopia.

(*c*) The corrected acuity of the "better" (less ametropic) eye decreases, although not strikingly, with increase in ametropia, the decrease being slightly more rapid in hyperopia than in myopia. The average does not fall below 20/20.

(*d*) The corrected acuity of the "worse" eye in myopia falls with increase in ametropia slightly more rapidly than that of its better fellow.

(*e*) The corrected acuity of the "worse" eye in hyperopia falls with increase of ametropia significantly more rapidly than the acuity for its better fellow or the acuity for either the "better" or the "worse" eye in myopia.

(*f*) In consequence, the average corrected acuity of hyperopic eyes is lower than that of myopic eyes, as has been reported by a number of workers. It should be emphasized that low corrected acuity tends to be characteristic only of the "worse" eye of the hyperopic nonstrabismic pair.

(g) Although unequal corrected acuity is associated with anisometropia, its greater incidence in hyperopia is not due to a greater incidence of anisometropia in this sample, since the occurrence of anisometropia does not differ significantly between the myopic and the hyperopic groups.

2. When sorting is done on the basis of ametropia differences between meridians and astigma differences, the following results were apparent:

(*a*) In the hyperopic sample there was a marked and statistically significant tendency toward lower corrected acuity in the eye with any or all of the following:

(1) Greater astigmia

(2) Greater ametropia in the vertical meridian

(3) Greater ametropia in the horizontal meridian

The strength of this association between corrected acuity differences and refractive differences is indexed by a multiple correlation coefficient of $R^2$=0.708.

(*b*) In the myopic sample there was a much less marked tendency of the same kind. Of the three kinds of refractive differences considered, only differences in astigmia yielded a statistically significant regression coefficient. The value of $R^2$ was 0.131, which, though statistically significant, is not large enough to indicate a very strong relationship between acuity difference and refractive differences.

3. Since only the relations at the time of examination, and not their development, are shown by the data, no direct light is thrown on the etiology of unequal corrected acuity in nonstrabismic patients. A longitudinal study of a large number of children from before the age of 6 to stable adult conditions is necessary to make clear the dynamics of unequal corrected acuity. Such a study is highly desirable.

(*a*) In the absence of any discontinuity in the distribution of acuities, or knowledge of the origin of the condition, or of its response to treatment, we have avoided the implications of the term "amblyopia" and have used

instead the noncommittal word "anisoxyopia" for the observed unequal corrected acuity.

(*b*) There is evidence that if the eye is deprived of clear images in early stages of development, at least before the age of 6 years, acuity seldom reaches normal levels, constituting the so-called "amblyopia of arrest." This may well have been a factor in the present cases, but, unfortunately, records are not complete enough either to prove or to disprove the point.

(*c*) It may be argued that if the anisometropia were not corrected early, the conditions would favor the differences observed between myopia and hyperopia. For if both eyes are myopic in different degrees, there exists for each eye a distance at which a clear image may be obtained without accommodation. On the other hand, in hyperopia no object at any distance may be clearly imaged without accommodation. For both near and far objects that amount of accommodation will probably be invoked which will give a clear image in the less hyperopic eye, and its more hyperopic fellow will never enjoy clear images.

(*d*) It is possible that the unequal corrected visual acuity observed had a mixed origin, involving other factors, such as suppression, aniseikonia, and optical effects. However, the hypothesis of accommodative posture in anisometropia which has not had early refractive correction is most appealing.

2400 Clay St.

## REFERENCES

1. Linksz, A.: Standard Visual Acuity Chart, Am. J. Ophth. **37**:803, 1954.

2. Weymouth, F. W., and Hirsch, M. J.: Relative Growth of the Eye, Am. J. Optom. & Arch. Am. Acad. Optom. **27**:317, 1950.

3. Broekema: Dissertation, Amsterdam, 1909; Jahresb. Leist. Ophth. **40**:782, 1909.

4. Juler, F.: Amblyopia from Disuse, Tr. Ophth. Soc. U. Kingdom **41**:129, 1921.

5. Copps, L. A.: Vision in Anisometropia, Am. J. Ophth. **27**:641, 1944.

## BIBLIOGRAPHY

Adler, F. H., and Fliegelman, M.: Influence of Fixation on the Visual Acuity, Arch. Ophth. **12**:475, 1934.

Barkan, H., and Borley, W. E.: Familial Cornea Plana, Complicated by Cataracta Nigra and Glaucoma, Am. J. Ophth. **19**:307, 1936.

Beauvieux, J., and Bessière, E.: Cranial Asymmetry in Unilateral Myopia, Bull. Soc. opht. France, p. 105, 1949.

Bourquin, A.: Incidence of Disease in Amblyopic Eyes, Ophthalmologica **125**:405, 1953.

Burian, H. M.: Amblyopia ex Anopsia: Its Nature and Essence, A. M. A. Arch. Ophth. **51**:413, 1954.

Cattaneo, D.: Study of Anisometropia, Ann. ottal. e clin. ocul. **55**:345, 1927.

Crawford, J. S.; Shagass, C., and Pashby, T. J.: Relationship Between Visual Acuity and Refractive Error in Myopia, Am. J. Ophth. **28**: 1220, 1945.

de Schweinitz, G.: Diseases of the Eye, Philadelphia, W. B. Saunders Company, 1924, p. 571.

Downing, A. H.: Ocular Defects in 60,000 Selectees, Arch. Ophth. **33**:137, 1945.

Eggers, H.: Estimation of Uncorrected Visual Acuity in Malingerers, Arch. Ophth. **33**:23, 1945.

Feldman, J. B.: Further Studies in Amblyopia, Am. J. Ophth. **32**:1394, 1949.

Ferree, C. E., and Rand, G.: The Testing of Visual Acuity, Am. J. Ophth. **17**:610, 1934.

Fink, W.: An Evaluation of Visual Acuity Symbols, Am. J. Ophth. **28**:701, 1945.

Fisher, E. M.: Amblyopia, Refraction and Accommodation, Sovet. vestnik oftal. **28**:30-33, 1949.

Ford, W. A.: Amblyopia, Wisconsin M. J. **39**: 278, 1940.

Frenkel, H.: Monolateral Myopia, Arch. opht. **45**:209, 1928.

Fry, G.: Significance of Visual Acuity Measurements Without Glasses, Am. J. Optom. **25**:199, 1948.

Glover, L. P.: Amblyopia in Identical Twins, Am. J. Ophth. **15**:140, 1932.

Granström, K. O.: Studies on Unilateral High Myopia, Acta ophth. **10**:348, 1932.

Hallett, J. W.: Amblyopia Independent of Usual Associated Conditions, A. M. A. Arch. Ophth. **45**:64, 1951.

Unexplained Amblyopia as a Military Problem, Mil. Surgeon **99**:110, 1946.

Hirsch, M. J.: Visual Acuity and Myopia, Arch. Ophth. **34**:418, 1945.

Irvine, S. R.: Amblyopia ex Anopsia Observations on Retinal Inhibitions, Scotoma, Projection, Light Difference Discrimination and Visual Acuity, Tr. Am. Ophth. Soc. **46**:527, 1948.

Koch, F. L. P., and Frangen, A. de H.: Marked Anisometropia, Arch. Ophth. **21**:987, 1939.

Kronfeld, P. C., and Devney, C.: The Frequency of Astigmatism, Arch. Ophth. **4**:873, 1930.

Lambert, R. K., and McDonnald, C. E.: Hereditary High Hyperopia, Am. J. Ophth. **14**:46, 1931.

Lazich, B. M.: Amblyopia ex Anopsia, Arch. Ophth. **39**:183, 1948.

Luckiesh, M., and Moss, F. K.: Effects of Astigmatism on the Visibility of Print, Am. J. Ophth. **26**:155, 1943.

McMullen, W. H.: Some Points on Anisometropia, Tr. Ophth. Soc. U. Kingdom **59**:119, 1939.

Morgan, G. E.: Amblyopia ex Anopsia in the Armed Forces, Am. J. Ophth. **29**:713, 1946.

Peter, L. C.: Amblyopia ex Anopsia in Adult Life, Am. J. Ophth. **15**:493, 1932.

Pincus, M. H.: Unaided Visual Acuities Correlated with Refractive Errors, Am. J. Ophth. **29**: 853, 1946.

Schmerl, E.: Higher Refractional Anomalies, Their Frequency in Different Groups and Countries, Am. J. Ophth. **32**:561, 1949.

Sloan, L. L.: Measurement of Visual Acuity, A. M. A. Arch. Ophth. **45**:704, 1951.

Sloane, A. E., and Gallagher, J. R.: Changes in Vision During Adolescence, Am. J. Ophth. **33**:1538, 1950.

Southgate, P. T.: High Hypermetropia, Am. J. Ophth. **33**:466, 1950.

Sugar, H. S.: Suppression Amblyopia, Am. J. Ophth. **27**:469, 1944.

Suo, K.: Unilateral Myopia, Nord. med. **9**:279, 1941.

Tron, E.: High Myopia with Good Vision, Sovet. vestnik oftal. **10**:19, 1937.

Vita, A.: Considerations and Researches on Retinal Relationships in Anisometropic Persons, Rass. ital. ottal. **2**:1037, 1933.

Waardenburg, P. J.: Anisometropia and Corneal Refraction, Klin. Monatsbl. Augenh. **84**:788, 1930.

Young, J. H.: Amblyopia ex Anopsia in Children, Brit. J. Ophth. **24**:297, 1940.

# Testing Distance Effect on Phoria Measurement at Various Accommodation Levels

MATHEW ALPERN, Ph.D., Ann Arbor, Mich.

An observer who sees one small point of light with one eye and a second small point of light (vertically displaced from the first) with the other is able to align the two spots with reasonable precision while reading a fine line of letters on a chart which is visible to one (and only one) of the two eyes.[1] The angular deviation of the lines from the centers of the observer's entrance pupils to the two lights from a horizontally parallel position at the time of alignment can be taken as a measure of the lateral phoria position. This position is influenced by a number of different stimulus conditions, including the accommodative state of the observer, the size of the test chart, and the distance from the observer to the test chart.

The variation in the magnitude of the phoria measurement as the accommodative state of the observer changes has been studied to some extent in the literature, and the clinical applications of some of the principles to discomfort and comfort in patients have been pointed out.[2] If care is taken to measure the reciprocal of the observer's conjugate focus (hereafter accommodative response) while measuring the phoria through different plus and minus lenses, it is found that the measurement indicates more esophoria as the accommodative response increases. A rough first approximation of this variation can usually be made by a straight line of positive slope.[3]

That the size of the stimulus pattern (in an otherwise darkened room) may also have a marked effect on the magnitude of both the phoria and the accommodative response has recently been pointed out by Ittleson and Ames.[4] Whether the obtained variation in phoria can be exclusively related to the changes in accommodation, or whether changes in the phoria with change in the size of the stimulus occur at a fixed accommodation response is largely a question that must be answered by further experiment.*

It has been known for some time that measurements of the phoria at different testing distances but at the same level of accommodation will give different results. This phenomenon has been studied to some extent, and a summary of the literature has recently been published by Schapero and Levy.[5] For a history of the problem and description of the early work reference is made to their paper. Measuring phorias in a different way from that described above, they found that, in general, as the testing distance decreased the measurement obtained at a fixed stimulus to accommodation was more esophoria. Unfortunately, they did not attempt to measure the accommodative response, and the degree the response varied at a fixed stimulus value is an uncertain variable which makes interpretation of the results rather difficult. The same criticism must be made of Asher's recent experiments.[2] Other experiments not subject to this criticism [6] have not been carried out at a variety of test distances, so that evidence is required in order to describe the way the phoria varies with test distance at a fixed accommodative response. The present experiments were designed to obtain such evidence.

Received for publication Sept. 22, 1955.

* Alpern, M.: Accommodation, Convergence and Their Relation to Apparent Distance: Further Comments, unpublished paper.

### APPARATUS

The apparatus used in the present experiments is essentially the same as that used by Morgan,[7] by Ittelson and Ames,[8] and by others. A detailed description by Ames, Gliddon, and Ogle† may be found in the literature, and so only the essential features will be described here. A line drawing is given in Figure 1. Two semisilvered mirrors are mounted on the arms of the haploscope, which rotate around vertical axes passing through the centers of rotation of the two eyes (*K* and *K'*). Each haploscope arm also contains a lens cell (*C* or *C'*), a lens (*L* or *L'*) of 122 mm. focal length, and a movable lamp housing (*H* or *H'*), which is completely opaque except for the pinpoint aperture (*X* or *X'*) on the side facing the lens. The far side of the mirror (*M'*) before the left eye

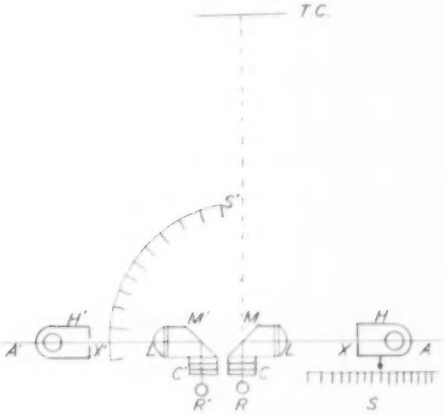



Fig. 1.—Diagram of the apparatus as seen from above.

was occluded so that the test chart (*T.C.*), illuminated by a 100 watt bulb, was seen only by the right eye. The observer saw two points of light superimposed on a test chart in front of him. Two scales were provided. One scale (*S*) gave the distance of the light point from the lens on the optical axis of the haploscope arm, and these values could be converted to values of accommodative response from a suitable calibration curve. The second scale (*S'*), the phoria scale, was calibrated in degrees and represented the angular deviation of the lines of sight of the two eyes in the horizontal plane.

### PROCEDURE

The observer was carefully positioned in the haploscope with the entrance pupil of each eye centered on the optic axis of each optical system so that a point on the line of sight 13 mm. behind each corneal apex was superimposed on the axis of rotation of each haploscope arm. The required spectacle correction was placed in the lens cells (*C* and *C'*), and the observer moved the light point before the left eye along the arm *A'* until it was seen at its smallest diameter. A vertical prism (5△ base up) was placed in the lens cell *C'* before the left eye so that this light point was displaced below that seen by the right eye. The observer then began to read the smallest visible row of letters on the test chart (at a distance of 590 cm. from the eye) and simultaneously adjusted the light point *X*, seen by the right eye, until it obtained its smallest possible diameter and rotated the haploscope arm *A'* before the left eye until the two lights were aligned vertically one above the other.‡ These data were recorded and the experiment was repeated three times. The stimulus to accommodation was increased by 1 D. by placing suitable trial case lenses before the right eye and the process repeated. The same procedure was followed with the stimulus to accommodation varied in the following order: 0, 1.00, 2.00, 3.00, 4.00, 4.50, 3.50, 2.50, 1.50, and 0.50 D. For most observers the entire routine required less than 20 minutes. After a suitable rest period the test chart was moved in to 200 cm. and the procedure was repeated. The test chart was then placed at 1 meter. This chart—instead of the standard size test chart used at the two previous test distances—was a photographically reduced test chart so designed that the smallest letters subtended 5 minutes at the entrance pupil when placed at 40 cm. This chart was used at all the near testing distances inside 1 meter. Measurements were made in the above way in the following order: 590, 200, 100, 66.65, 50, 40, 33.33, 28.6, 25, 22.2, and 20 cm. from the observer's spectacle plane. Data were obtained on 11 young adults.

### RESULTS

The data for each testing distance for each observer were plotted on a graph showing the variation in the phoria as a function of the accommodative response. Typical data for a single observer are plotted in Figure 2. In each graph, the ordinates are values of accommodative response in diopters, while the abscissa values are the obtained phoria measurements in degrees of positive convergence increasing toward the right. The plotted points are the means of three measurements. The graphs are so arranged that each graph, beginning at the top and going

† References 8 and 9.

‡ Westheimer [10] estimates the precision of such measurements to be ±0.25 D. for each accommodation measurement and ±0.25△ for each phoria measurement.

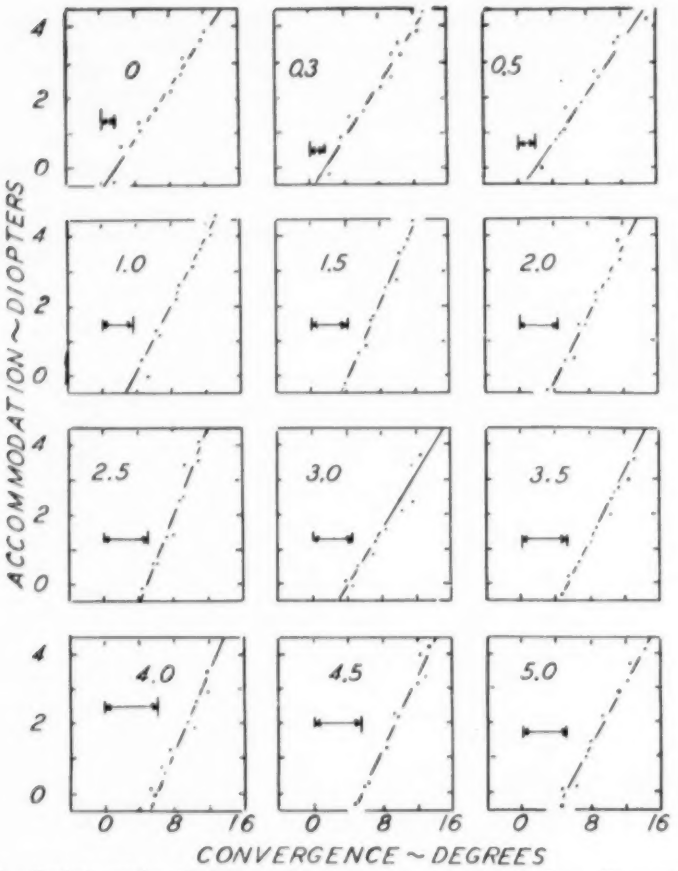



Fig. 2.—Typical results of the experiment on one observer (A. R.). The ordinates of each graph represent accommodative responses, and the abscissas are values of the phoria in degrees (increasing esophoria toward the right.) Beginning at the top and going from right to left, each graph represents data obtained at successively closer testing distances. The number in each graph represents the reciprocal of the testing distance in meters. The points are the means of three independent measurements, while the straight lines have been fitted to the data by the method of least squares. The horizontal line on each graph shows the magnitude of the phoria at zero accommodative response.

from left to right, is associated with successively closer testing distances. The reciprocal of the testing distance in meters is given in each figure for identification. It is apparent from the data that the variation in phoria with accommodative response is quite reasonably described by a straight line of positive slope. This proved to be true for each of the 11 observers studied in the present experiments. The best-fitting straight line for each set of data and for each of the observers was calculated, using the method of least squares. It is this line which has been drawn in on each of the graphs in Figure 2.

Since the data in Figure 2 are exactly typical of data obtained from the other observers, and since in each case the data are adequately described by straight lines, figures like those in Figure 2 are not presented for the other observers. Instead, in the interest of conservation of space, only the characteristics of the computed best-fitting straight line are presented. A straight line can be described completely by only two constants. For the present purpose the two

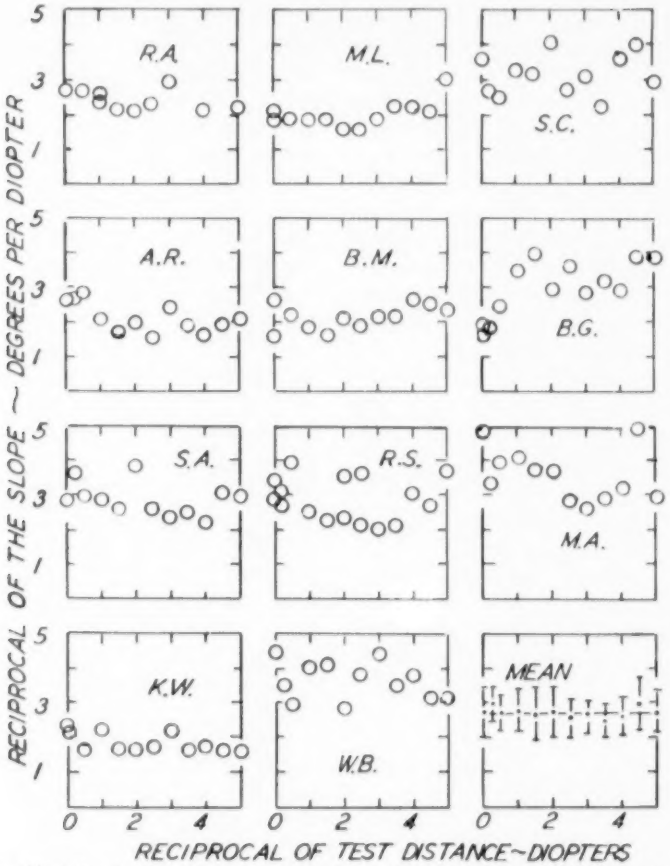



Fig. 3.—Variation in the reciprocal of the slope of the best-fitting straight lines as a function of the testing distance for each of the 11 observers. Ordinates represent reciprocal of the slope in degrees per diopter; abscissas, reciprocal of the testing distance in meters. The lower right-hand graph presents the mean of the results for the 11 observers, together with the average deviation.

constants more or less arbitrarily selected are (*a*) the reciprocal of the slope in degrees of phoria change per diopter of accommodation and (*b*) the phoria value for zero accommodative response.

*The Reciprocal of the Slope.*—This was selected, since it represents a value which has been studied at some length and is utilized clinically in the formulation of the patient's prescription.[7] Morgan refers to it as the AC/A, i. e., the accommodative convergence associated with each diopter change in accommodation. The variation in the reciprocal of the slope with testing distance for each of the observers is plotted in Figure 3. In this Figure, each graph gives the results from a different observer. The ordinates in each curve represent values of the reciprocal of the slope in degrees increase in phoria per diopter of accommodative response, while the abscissas are values of the reciprocals of the testing distance in meters.

For each observer there was a marked random variation in the AC/A. Are these variations merely a product of poor precision in the individual measurements of accommodative response and phoria? Each value for the AC/A was calculated from 30 reasonably precise measurements, and it appeared unlikely that such wide variability

could be attributed to this lack of precision. Nevertheless, a further statistical analysis of the data of the observer A. R. (whose individual measurements are illustrated in Figure 2) was made in order to give a definite answer to this question. It should be emphasized that the magnitude of the random variations in AC/A for A. R. were neither the largest nor the smallest of those obtained but represented, rather, typical data for the group. For each testing distance the standard deviation of the regression coefficient was calculated for the best-fitting straight line, and from these data the 95% limits of confidence ranges of AC/A were determined. These results are summarized in

TABLE 1.—*Statistical Analysis of AC/A Values for Subject A. R.*

| Testing Distance, Cm. | AC/A Degrees/ Diopters | 95% Limits |
|---|---|---|
| 500 | 2.64 | ± 0.18 |
| 300 | 2.65 | ± 0.26 |
| 200 | 2.81 | ± 0.24 |
| 100 | 2.15 | ± 0.20 |
| 67 | 1.74 | ± 0.12 |
| 50 | 2.05 | ± 0.20 |
| 40 | 1.56 | ± 0.22 |
| 33 | 2.41 | ± 0.32 |
| 29 | 1.94 | ± 0.12 |
| 25 | 1.68 | ± 0.15 |
| 22 | 1.95 | ± 0.19 |
| 20 | 2.19 | ± 0.17 |
| Mean | 2.14 | ± 0.19 |

Table 1, in which the first column gives the testing distance in centimeters, the second column gives the AC/A (degrees per diopter) as determined by the reciprocal of the slope of the best-fitting straight line determined by the method of least squares, and the third column gives the extent of the 95% confidence range of the AC/A (degrees per diopter) as calculated from the standard deviation of the regression coefficient. It is apparent from even a cursory glance at Table 1 that the random variations in AC/A were much larger than the extent of the range of the 95% limits of confidence. Clearly, the problem is one of the reliability of the haploscopic measurement of the AC/A as a whole rather than the precision of the individual measurements of accommodation and phoria.

In order to remove the effect of different testing distances, a few measurements were made of a test-retest nature at the same testing distance. These data confirmed the random fluctuation of the AC/A shown in Table 1 and Figure 3. For example, for Subject R. W. S. measurement at 40 cm. revealed a calculated AC/A (by method of least squares) of 2.29°/D, with the 95% confidence range limits of 2.17°/D (lower) and 2.42°/D (upper). However, repetition of the same procedure under conditions as nearly alike as it was possible to obtain yielded a retest AC/A (calculated by the method of least squares) of 3.67°/D, with the 95% confidence range limits (somewhat larger) of 3.11°/D (lower) and 4.50°/D (upper). Such data emphasize the necessity of a detailed haploscopic study of variation of AC/A in a single observer under constant viewing conditions.

The random fluctuations in AC/A as obtained in this study throw some light on the seemingly contradictory results recently reported by Westheimer.[10] Using similar testing procedures, at a single (20 ft.) testing distance, he found that the obtained relationship between phoria and accommodative response (in two observers) could sometimes be better described by a quadratic (i. e., curvilinear rather than a linear) equation. Detailed analysis of his procedure § indicated, however, that his individual determinations were made over a more extended period of time than in the present study. If the random variations in AC/A as described in the present study were operating in his experiment, a curvilinear relationship might readily have been obtained over an extended testing period where more rapid measurements (complete within 20 minutes) might reveal straight lines. Such speculations can only be verified by further experiment.

The wide variation in the same experienced observer in successive measurements of AC/A found with the haploscope is not anticipated on the basis of current theory, which treats such data as though they were reasonably invariant.‖ Since these values

§ Westheimer, G.: Personal communication to the authors.

‖ References 11 to 13.

were obtained by statistically fitting each of 30 measurements (in which both accommodative response and convergence are more precisely measured than in the usual clinical situation) with straight lines, these fluctuations also lend some question as to the extent to which we can rely on the clinical measurements of the AC/A as a major factor in the diagnosis and treatment of discomfort symptoms.[7] Both these theoretical and clinical implications of the present findings must await further experiment, however, before adequate revision of theory and practice may be attempted. It is sufficient for the present purposes to point out the inconsistencies that they represent.

Leaving aside, then, these random fluctuations of the AC/A, there does not appear to be any consistent variation in slope with testing distance. As a first approximation, the most reasonable assumption seems to be that the AC/A ratio is relatively independent of the testing distance. This is true not only for the measurements on each individual observer but also for the average of the results of all of the observers. These latter findings (together with their average deviations) have been plotted in the lower right-hand graph in Figure 3. These results are in agreement with some data reported by Morgan [3] but differ somewhat from the findings of Schapero and Levy,[5] who studied the variation in phoria with variation in the stimulus to accommodation. They found that the slope of the phoria line increased as the testing distance decreased. It seems reasonable to attribute this discrepancy to the fact that Schapero and Levy investigated the relationship of phoria to the accommodative stimulus rather than to the response.

*Phoria Value for Zero Accommodative Response.*—Since the general pattern of the slope remains relatively unchanged with testing distance, the effect of testing distance may be studied by observing the manner in which the phoria at any given accommodative response level varies. For the sake of convenience, the value of zero accommodative response has been arbitrarily selected, since this value would correspond to the phoria clinically measured at infinity. The way that this value changes for the observer whose data are illustrated in Figure 2 may be obtained from the length of the horizontal line drawn in each of the graphs in that Figure. The data for each of the observers has been summarized in Figure 4. In this figure each graph represents the results for a different observer. The ordinates in these graphs represent the changes in the zero level phorias (assuming the most distant zero level phoria as zero) in degrees, while the abscissas are values for the reciprocal of the testing distances in meters. For the sake of comparison, then, each graph begins at the extreme left at the zero level of phoria. The absolute value of the zero level phoria at the greatest testing distance is given in each of the graphs (plus values indicate esophoria; minus values indicate exophoria).

The most important conclusion which may be derived by inspection of the data is that there were marked individual differences in the way in which the zero level phoria changed with decrease of testing distance. Some of the observers showed a marked increase (i.e., more esophoria) in the zero level phoria; others showed a slight decrease in zero level phoria with testing distance, while still others showed virtually no change in the zero level phoria with testing distance. The data for the observers do not seem to group themselves into definite categories. Rather, the patterns of response appear to be spread out on a continuum. At the one extreme may be found observers who showed a slight decrease in phoria with decrease in testing distance (B. G.). Other observers showed no very marked change in phoria with decrease in testing distance (S.C., W.B., and R.S.). At the other extreme are these who showed a marked increase in phoria with decrease in testing distance (S. A., M. L., A. R., R. A., and, especially, M. A.). Virtually every stage between the extremes is represented by the observers studied in these experiments. The way in which the phoria changed with testing distance in each of the observers does not appear to be related in any obvious way to the absolute value of the

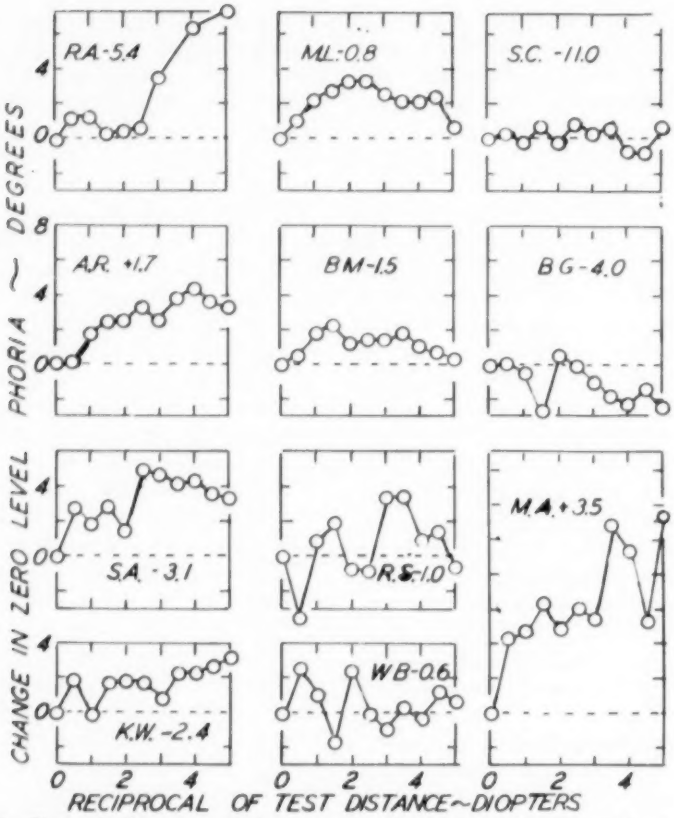



Fig. 4.—Change in the zero level phoria as a function of the testing distance for each of the 11 observers. The zero level phoria at the largest testing distance has been arbitrarily set at zero, and the rest of the data have been changed accordingly. The absolute value of the zero level phoria at the largest testing distance is given in each graph (positive values represent esophoria). Ordinates represent change in the zero level phoria; abscissas, reciprocal of the testing distance in meters.

zero level phoria at the farthest testing distance, to the age of the observer, or to the type of spectacle correction that he required.

The marked individual differences of these data emphasize the danger of attempting to obtain conclusions by averaging the results of such experiments on a large number of subjects. This may most easily be illustrated by study of the data in Figure 5. These data are the mean changes in the zero level phoria of the 11 observers in the present study. The ordinates are the averages of the changes in the zero level phoria, while the abscissas are the reciprocals of the testing distance in meters. Although the mean data showed a rather linear increase in phoria as the reciprocal of the testing distance increased (at least through the middle testing distances), this pattern was not followed with any regularity by any of the 11 observers. The mean data suggest that changes of phoria with distance much larger than 5Δ would not be anticipated. It is only when the data for each individual observer are studied that the rather marked effect of the testing distance on the phoria becomes apparent. It should perhaps be added that, while the mean data in Figure 5 do not reflect the pattern of any of the 11 observers in the present study, they are similar to results described by Morgan [7] on an unspecified observer or observers under more limited testing conditions.

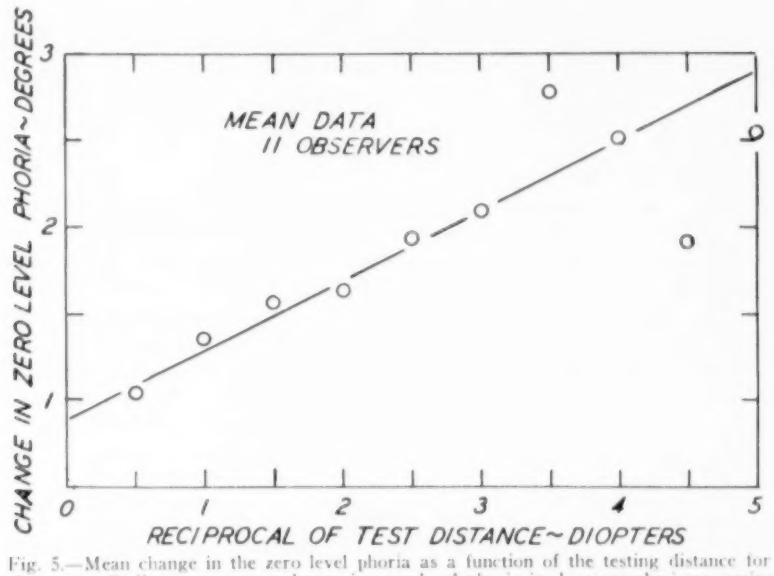



Fig. 5.—Mean change in the zero level phoria as a function of the testing distance for the 11 observers. Ordinates represent change in zero level phoria in degrees; abscissas, reciprocal of the testing distance in meters.

Does the nearer testing distance increase the accommodative response to a given stimulus to accommodation? In order to answer this question, the average of the accommodative responses was compared with the average stimulus to accommodation for each testing distance. The data for the individual observers all showed the same general trends. The average value for the accommodative stimulus minus the accommodative response for each individual measurement and for all of the observers, together with the average deviations of these measurements, is shown for each testing distance in Table 2. Clearly, no very marked increase in the accommodative response occurs with decrease in the testing distance. These results are in agreement with the findings of other investigators, who studied only two testing distances.¶

TABLE 2.—*Relation of Test Distance to Accommodation Response*

| Test Distance, Cm. | Accommodative Stimulus Minus Response in Diopters | |
|---|---|---|
| | Mean * | Average Deviation |
| 500 | 0.38 | ± 0.30 |
| 300 | 0.56 | ± 0.29 |
| 200 | 0.56 | ± 0.28 |
| 100 | 0.53 | ± 0.30 |
| 67 | 0.44 | ± 0.26 |
| 50 | 0.44 | ± 0.38 |
| 40 | 0.39 | ± 0.36 |
| 33 | 0.35 | ± 0.27 |
| 29 | 0.54 | ± 0.42 |
| 25 | 0.44 | ± 0.24 |
| 22 | 0.34 | ± 0.21 |
| 20 | 0.33 | ± 0.31 |

* Mean for 11 observers.

## COMMENT

One important implication of the present results should be pointed out. Although the observers who showed some increase in the zero level phoria with decrease in test distance could not be separated from the other observers with a common factor of age, zero level distance phoria, or spectacle correction, there was one way in which many of these observers could be separated from the rest of the group. This was in the history of evidence of reduction in binocular vision. The observer M. A., who showed the most prominent increase in the zero level phoria with decrease in the testing distance, was the only strabismic of the 11 observers. A somewhat detailed description of the visual characteristics of this observer has been made elsewhere.[14] However, Observer A. R. has a history of esotropia at an early age which has been corrected, while Observers

¶ References 3 and 6.

R. A., M. L., and K. W. all show some evidence of inefficient binocular vision, as evidenced by clinic measurements of stereopsis or suppression. It seems worthy of pointing out that all of these observers showed a definite increase in the zero level phoria as testing distance decreased. This aspect of the problem can be applied in a clinical way only after a more detailed investigation. Such questions as, "Does the continuum of patterns of change of zero level phoria with testing distance suggest a continuum of individuals at various levels of binocular performance?" must await such investigations for an answer. Multiple distance phoria testing may yet prove of definite diagnostic value clinically, but clearly the present experiments cannot be used to provide the criteria for such diagnosis.

The finding that very pronounced increases in zero level phoria with testing distance occurred in a strabismic observer (as well as observers with imperfect binocular vision) seems to run contrary to the notion # that such increases are most closely related to what has been called fusional convergence.[16] According to this latter speculation, it would scarcely be expected that an observer who fails to demonstrate any fusional movements (in the usual sense of the word) would show the most pronounced increase of zero level phoria with decrease of testing distance of all the observers studied.*

Contrariwise, the notion may be ventured that some such patterns of increased "convergence" to near distances are more likely to occur in strabismic observers, increasing thereby the flexibility of whatever binocular apparatus still persists. Such speculations certainly cannot be labored at any length at the present stage of our ignorance of these phenomena, but they do seem to command further consideration.

Finally, mention should be made of the size-distance relationship as it might influence the data of the present experiments. In measuring the effects of distance on the phoria, it is possible to keep constant either (*a*) the apparent (i. e., the angular) size of the test object or (*b*) the physical size of the test object. A third possibility, that of keeping the perceived size constant, would represent a compromise between the two if the data of size constancy[19] are applicable to the present experimental design. The present experiments were done by using two targets of different physical size (a standard test chart at test distances 590, 300, and 200 cm. and a photographically reduced test chart for all closer distances). This represents a qualitative approach to the above compromise. Whether or not this procedure is the most heuristic of those available can only be answered by further experiment. Preliminary experiments along this line will be described subsequently.†

University of Michigan.

# References 7 and 15.

* While it is true that certain kinds of responses to disparate stimuli can be obtained in patients with permanent strabismus, there are important differences which differentiate these from the fusional movements obtained in normal observers (References 14, 17, and 18).

† Alpern, M.: Accommodation, Convergence and Their Relation to Apparent Distance: Further Comments, unpublished paper.

REFERENCES

1. Morgan, M. W., Jr.: The Clinical Aspects of Accommodation and Convergence, Am. J. Optom. **21**:304, 1944.

2. Asher, H.: Stimulus to Convergence in Normal and Asthenopic Subjects, Brit. J. Ophth. **36**:666-675, 1952.

3. Morgan, M. W., Jr.: Accommodation and Its Relationship to Convergence, Am. J. Optom. **21**:191, 1944.

4. Ittelson, W. H., and Ames, A., Jr.: Accommodation, Convergence and Their Relation to Apparent Distance, J. Psychol. **30**:43-62, 1950.

5. Schapero, M., and Levy, M.: The Variation of Proximal Convergence with Change in Distance, Am. J. Optom. **30**:403-416, 1953.

6. Hofstetter, H. W.: The Proximal Factor in Accommodation and Convergence, Am. J. Optom. **19**:67, 1942.

7. Morgan, M. W., Jr.: Relationship Between Accommodation and Convergence, A. M. A. Arch. Ophth. **47**:745-759, 1952.

8. Ames, A., Jr.; Gliddon, G. H., and Ogle, K. N.: Size and Shape of Ocular Images, Arch. Ophth. **7**:8, 1932.

9. Ames, A., Jr., and Gliddon, G. H.: Ocular Measurements, Tr. Sect. Ophth. A. M. A. **26**:102, 1928.

10. Westheimer, G.: The Relationship Between Accommodation and Accommodative Convergence, Am. J. Optom. **32**:206-212, 1955.

11. Alpern, M.: The Zone of Clear Single Vision at the Upper Levels of Accommodation and Convergence, Am. J. Optom. **27**:491-513, 1950.

12. Alpern, M.: Probing Problems of Presbyopia, O-Eye-O **17**:24-29, 1951.

13. Hofstetter, H. W.: The Zone of Clear Single Binocular Vision, Am. J. Optom. **22**:361, 1945.

14. Alpern, M., and Hofstetter, H. W.: The Effect of Prism on Esotropia: A Case Report, Am. J. Optom, Monograph 41, 1948, pp. 1-12.

15. Hofstetter, H. W.: The Relationship of Proximal Convergence to Fusional and Accommodative Convergence, Am. J. Optom. **28**:300, 1951.

16. Maddox, E. C.: The Clinical Use of Prisms and the Decentering of Lenses, Ed. 2, Bristol, John Wright & Co., 1893, p. 106.

17. Burian, H. M.: Fusional Movements in Permanent Strabismus, Arch. Ophth. **26**:626-650, 1941.

18. Hallden, Ulf: Fusional Phenomena in Anomalous Correspondence, Acta ophth., Supp. 37, 1952.

19. Koffka, K.: Principles of Gestalt Pyschology, New York, Harcourt, Brace and Company, Inc., 1935, pp. 87-95, especially p. 92.

# News and Comment

## SOCIETY NEWS

**The Ophthalmological Society of the United Kingdom.**— The Annual Congress of the Ophthalmological Society of the United Kingdom will be held at the Royal Society of Medicine, 1 Wimpole St., London, W.1, on April 26, 27, and 28, 1956.

The subject for discussion will be "The Early Diagnosis of Glaucoma." Members who wish to take part in the subsequent discussion are advised to intimate their intention before the opening of the Congress. It is emphasized that no member may speak for more than 10 minutes.

There will also be a short symposium on "Herpetic Infections of the Outer Eye."

Members wishing to read a short paper or to give a short pictorial demonstration are asked to send the title, together with an abstract, to Mr. Cook not later than Nov. 30, 1955. Those wishing to show films should also communicate with Mr. Cook by the same date.

The annual dinner will be held on Thursday, April 26. Members may bring guests.

A Trade Exhibition will be held in Cowdray Hall (next door to the Royal Society of Medicine).

On account of the difficulty in obtaining hotel accommodation in London, all members who will require it are advised to make their arrangements in good time. Honorary Secretaries: Derek Ainslie (Council Business); C. A. Cook (Congress Business).

**St. Louis Ophthalmological Society.**—The regular meetings of the St. Louis Ophthalmological Society will be held on the following Thursdays of this fiscal year.

| | |
|---|---|
| Oct. 27, 1955 | Feb. 23, 1956 |
| Dec. 1, 1955 | March 22, 1956 |
| Jan. 26, 1956 | April 26, 1956 |

The meeting place is the Park Plaza Hotel, 220 N. Kingshighway.

## CORRECTION

In the Special Report, "Estimation of Loss of Visual Efficiency," by Edmund B. Spaeth, F. Bruce Fralick, and William F. Hughes Jr., in the September, 1955, issue of the ARCHIVES, an error in percentage calculation appears in Section V, page 467. The result of multiplying 0.30 by 0.40 by 0.70 is 0.084, not 0.84 as stated in the text. The total visual efficiency of this eye is correctly given in the Report as 8.4%.

# Intraocular Penetration of Locally Applied Steroids

IRVING H. LEOPOLD, M.D.
JOHN L. SAWYER
and
HARRY GREEN, Ph.D., Philadelphia

Hydrocortisone acetate (Compound F acetate) has been shown to be superior to cortisone acetate (Compound E acetate) as an antiphlogistic agent in the treatment of many external ocular lesions, such as vernal conjunctivitis and episcleritis. This superiority, however, is not apparent in the treatment of anterior segment intraocular inflammation, such as uveitis, by local instillation of drops.* The free-alcohol form of hydrocortisone is considered to be more effective than the acetate in the treatment of intraocular lesions by local administration.†

In a recent publication from this laboratory [4] it was shown that hydrocortisone acetate entered the anterior chamber of rabbit eyes less rapidly and to a less extent than did cortisone acetate after local application. This observation may explain the difference in the relative efficacy of the two steroid acetates in the treatment of intraocular inflammation. If the extent of penetration of the drug is an important determinant of the clinical results, then one should expect the free-alcohol form of hydrocortisone to penetrate the anterior chamber more readily than the acetate. The present investigation was initiated in order to determine whether such a correlation exists. In addition, penetration studies were made with the free alcohol and acetate of fludrocortisone (9α-fluorohydrocortisone, 9FF), which clinically appears to possess anti-inflammatory action at lower concentrations than that required by hydrocortisone.

Received for publication Oct. 10, 1955.

Wills Eye Hospital, Department of Research.

This investigation was supported in part by a research grant from the National Institute of Neurological Diseases and Blindness, of the National Institutes of Health, U. S. Public Health Service.

* References 1 and 2.

† References 3 and 4.

## MATERIALS

The corticosteroids were supplied by Sharp & Dohme and Chemical Divisions of Merck & Co., Inc. The acetates of cortisone and hydrocortisone were supplied as 2.5% saline suspensions; that of fludrocortisone, as well as the free alcohols of the corticosteroids, were supplied as purified crystalline compounds. Suspensions of the latter were prepared in saline solution containing 1 : 40,000 benzalkonium chloride, after the compounds were ground to a fine powder in a mortar with pestle. Dilutions of the stock suspensions were made with saline solution.

All reagent chemicals were of analytical reagent grade. Chloroform was redistilled before use. Methanol (anhydrous) and ethanol (95%) were used without prior treatment. Phenylhydrazine hydrochloride and tetramethylammonium hydroxide were Eastman Kodak products; blue tetrazolium was supplied by Nutritional Biochemicals Corporation.

## PROCEDURE

Normal eyes of adult pigmented rabbits, 5½ to 6½ lb. in weight, were used. Removal and extraction of the aqueous humor were done as previously described.[4] In all cases 0.2 ml. of aqueous humor from each eye was extracted four times with 5 ml. portions of chloroform. Analyses were performed by the blue tetrazolium test as recently modified.[5] In some cases the Porter-Silber test was employed.

Two drops of the corticosteroid suspension were applied to the cornea every 15 minutes for one hour. Fifteen minutes after the last application the eye was flushed thoroughly with tap water and the anterior chamber tapped. After subconjunctival injections 30 minutes elapsed before the aqueous humor was removed.

*Abrasion of Cornea.*—This was accomplished by gently rubbing a cotton applicator over the anesthetized cornea. Removal of the epithelium was complete, as indicated by staining with fluorescein.

*Alkali Burns.*—One drop of 4% NaOH was dropped upon the cornea; 15 minutes later the eye was thoroughly flushed with tap water.

TABLE 1.—*Determination of Blue-Tetrazolium-Positive Material in Aqueous Humor of Normal Eyes and Alkali-Burned Eyes**

| | Normal Eyes | Alkali-Burned Eyes |
|---|---|---|
| | 0.077 | 0.049 |
| | 0.038 | 0.016 |
| | 0.029 | 0.102 |
| | 0.011 | 0.042 |
| | 0.012 | 0.068 |
| | 0.033 | 0.050 |
| | .... | 0.088 |
| Av. | 0.033 | 0.059 |

* Optical density at 510 mμ; 0.2 ml. aqueous humor.

TABLE 2.—*Penetration of Acetates of Corticosteroids, Cortisone, Hydrocortisone, and Fludrocortisone into Aqueous Humor, 0.2 Ml.*

| | Cortisone,* γ/0.2 Ml. | Hydrocortisone, γ/0.2 Ml. | Fludrocortisone, γ/0.2 Ml. |
|---|---|---|---|
| | A. Subconjunctival Injection—25 Mg. Steroid in 0.5 Ml. Saline | | |
| | 2.09 | 0.29 | 0.54 |
| | 0.18 | 0.27 | 0.91 |
| | 0.07 | 0.22 | 0.31 |
| | 1.35 | 0.42 | 0.00 |
| Av. | 0.92 | 0.30 | 0.44 |
| | B. Normal Corneas—Treated with 0.5% Suspension of Steroid | | |
| | 0.00 | 0.25 | 1.78 0.92 |
| | 0.73 | 0.43 | 0.63 1.20 |
| | 0.00 | 0.00 | 1.03 0.80 |
| | 0.00 | 0.00 | 1.09 1.13 |
| | .... | 0.11 | 0.80 0.82 |
| Av. | 0.18 | 0.28 | 1.08 |
| | C. Abraded Corneas—Treated with 0.5% Suspension of Steroid | | |
| | 1.78 | 0.54 | 1.74 |
| | 2.26 | 0.42 | 0.91 |
| | 0.69 | 0.73 | 1.27 |
| | 0.27 | 0.64 | 1.07 |
| | 2.87 | .... | .... |
| Av. | 1.57 | 0.58 | 1.25 |
| | D. Alkali-Burned Corneas—Treated with 0.5% Suspension of Steroid | | |
| | 0.67 | 0.75 | 1.18 |
| | 1.50 | 2.06 | 1.55 |
| | 5.74 | 0.49 | 0.64 |
| | 1.05 | 0.33 | 0.00 |
| | 1.33 | 0.00 | .... |
| | .... | 0.64 | .... |
| Av. | 2.06 | 0.71 | 0.69 |
| | E. Alkali-Burned Corneas—Treated with 2.5% Suspension of Steroid | | |
| | 2.69 | 0.07 | .... |
| | 3.56 | 0.00 | .... |
| | 2.73 | 0.86 | .... |
| | 2.02 | 1.71 | .... |
| | 3.73 | 0.00 | .... |
| | 3.05 | 0.62 | .... |
| | .... | 0.44 | .... |
| Av. | 2.96 | 0.61 | .... |

* Injection of 8 mg.

## RESULTS

The results are given in Tables 1 to 3 and represent values obtained with the chloroform extract of 0.2 ml. of aqueous humor. The optical density equivalent per 1γ of steroid by the blue tetrazolium test at 510 mμ is 0.055 for each of the materials tested. The Porter-Silber test is less sensitive for the hydrocortisones than for cortisone; the optical density equivalents per 1γ of steroid are as follows: cortisone, 0.047; hydrocortisone, 0.025; fludrocortisone, 0.024. In all experiments the observed optical density was corrected for the average optical density obtained with the aqueous humor from an untreated eye or from an alkali-burned eye, as the case may be. These correction values are given in Table 1 and show that the

TABLE 3.—*Penetration of Free Alcohols of Corticosteroids, Cortisone, Hydrocortisone, and Fludrocortisone into Aqueous Humor, 0.2 Ml.*

| | Cortisone, γ/0.2 Ml. | Hydrocortisone, γ/0.2 Ml. | Fludrocortisone, γ/0.2 Ml. |
|---|---|---|---|
| | A. Subconjunctival Injection—25 Mg. Steroid in 0.5 Ml. Saline | | |
| | 0.14 | 1.09 | 1.89 |
| | 0.09 | 1.87 | 1.25 |
| | 0.16 | 0.18 | 0.00 |
| | .... | 0.20 | 0.69 |
| | .... | .... | 0.52 |
| Av. | 0.15 | 0.84 | 0.87 |
| | B. Normal Corneas—Treated with 0.5% Suspension of Steroid | | |
| | 2.65 | 1.22 | 0.40 |
| | 1.63 | 0.00 | 0.56 |
| | 2.14 | 0.80 | 0.92 |
| | 2.16 | 2.12 | 1.40 |
| | 1.89 | 1.13 | 1.33 |
| | .... | .... | 0.89 |
| Av. | 1.97 | 1.05 | 0.91 |
| | C. Abraded Corneas—Treated with 0.5% Suspension of Steroid | | |
| | 0.00 | 3.12 3.17 | 1.42 |
| | 0.00 | 5.20 4.38 | 1.93 |
| | 2.58 | 7.52 3.15 | 0.09 |
| | 0.91 | 8.72 3.60 | 0.87 |
| | 3.81 | 5.25 2.82 | 0.29 |
| | 0.60 | 6.35 2.20 | 1.56 |
| Av. | 1.09 | 4.62 | 1.12 |
| | D. Alkali-Burned Corneas—Treated with 0.5% Suspension of Steroid | | |
| | 2.93 | 7.08 | 1.65 |
| | 2.82 | 1.60 | 6.06 |
| | 1.45 | 5.75 | 1.45 |
| | 2.60 | 2.27 | 2.62 |
| | 3.80 | 5.47 | 4.25 |
| Av. | 2.74 | 4.43 | 3.21 |

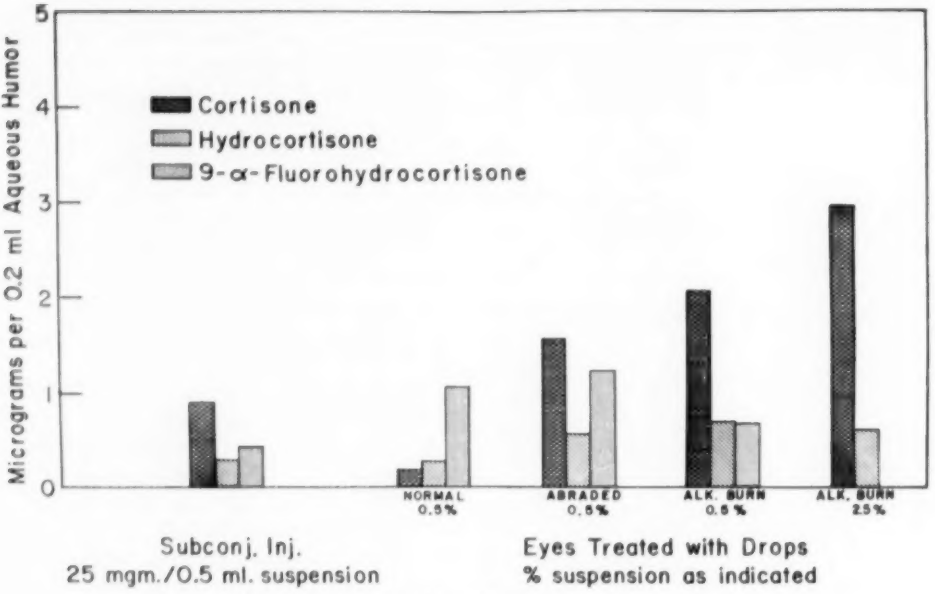



Fig. 1.—Penetration of steroid acetates locally applied.

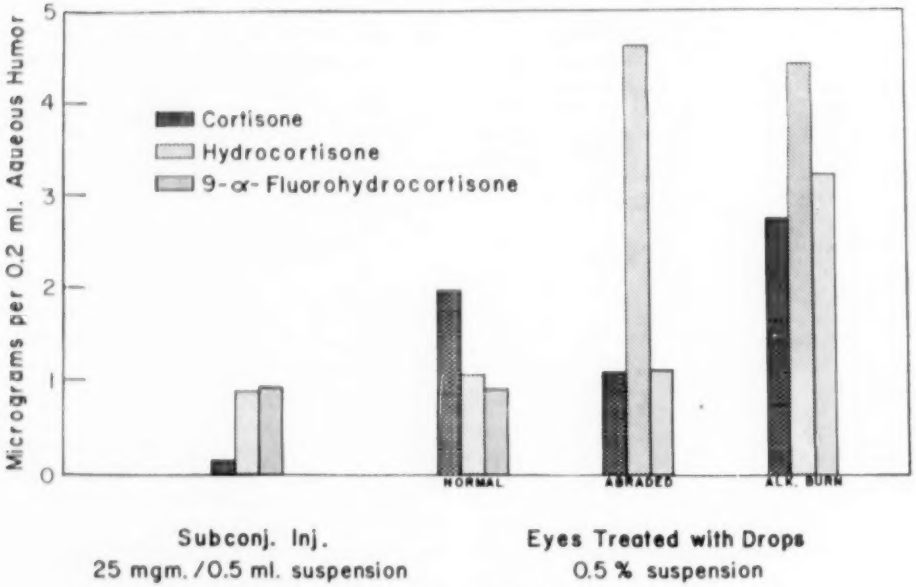



Fig. 2.—Penetration of steroid alcohols locally applied.

average optical density for the untreated eyes is 0.033 and that for alkali-burned eyes is 0.059.

For ease of comparison, the results are graphically presented in Figures 1, 2, and 3.

*Comparison of the Acetate and Alcohol of Each Steroid* (Fig. 1).—From a study of the accompanying Tables and Graphs, it is evident that, in the normal eye, after subconjunctival injection cortisone acetate pene-

trated more readily than the free alcohol, whereas the free alcohol of hydrocortisone penetrated more readily than the acetate form. Fludrocortisone behaved similarly to hydrocortisone.

When the steroids were applied as drops, cortisone alcohol penetrated to a greater extent than the acetate. This was also true for hydrocortisone, while fludrocortisone gave approximately the same results with both the acetate and the free alcohol. With eyes whose epithelial barrier had been removed, the acetate of fludrocortisone all the steroids showed higher penetration in the inflamed eye than in the normal eye.

It is also apparent that the free-alcohol forms of cortisone and hydrocortisone penetrate the normal eye after drop instillation better than the corresponding acetates, while the acetate of fludrocortisone is slightly superior to the free-alcohol form.

*Comparison of the Acetates of the Steroids* (Fig. 2).—It is evident from the data that, except for instillation in normal eyes, corti-

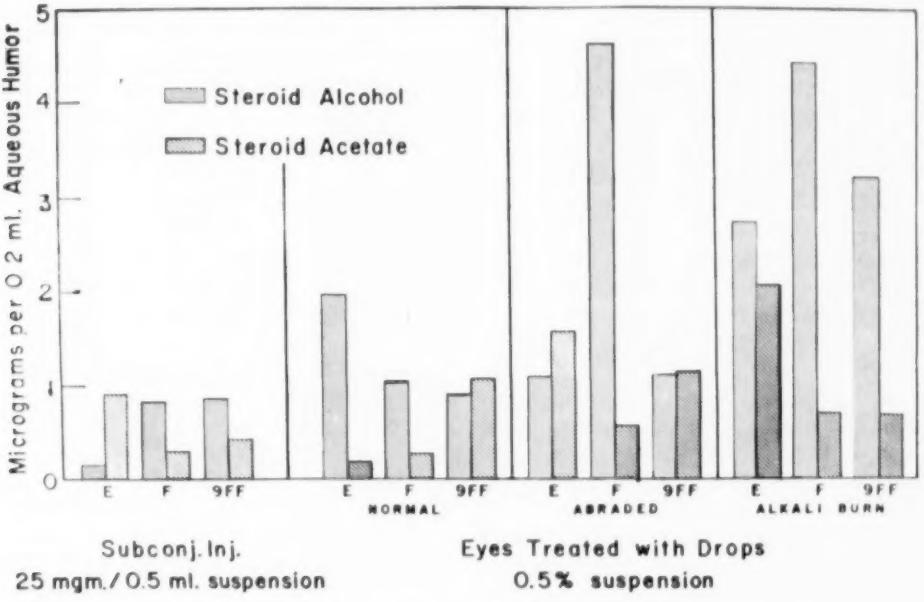



Fig. 3.—Penetration of steroids locally applied.

the outstanding feature was much greater penetration of the free alcohol of hydrocortisone. The acetate and free-alcohol form of cortisone and of fludrocortisone penetrated to practically the same extent.

With eyes that had been inflamed by the instillation of alkali the penetration of the free alcohol of hydrocortisone was again quite pronounced. In general, under these conditions the free-alcohol forms of the three steroids tested entered the aqueous humor to a greater extent than did the corresponding acetates. It is also apparent that except for sone acetate penetrated two to three times as much as the acetates of hydrocortisone and fludrocortisone after subconjunctival injection in normal eyes and after drop instillation in eyes whose epithelium had been removed or in which inflammation was caused by alkali burn. With normal eyes after drop instillation fludrocortisone acetate penetrated to the greatest extent, while the acetates of cortisone and hydrocortisone penetrated to a negligible extent. Fludrocortisone acetate penetrated somewhat better than hydrocortisone acetate in eyes without epi-

thelium, while with alkali-burned eyes the two steroid acetates behaved alike. It is interesting to note that by increasing the concentration of the drops from 0.5% to 2.5% of steroid acetate content, the penetration of cortisone acetate in alkali-burned eyes was somewhat increased, while that of hydrocortisone acetate was unaffected.

*Comparison of the Alcohols of the Steroids* (Fig. 3).—The alcohols of hydrocortisone and fludrocortisone both penetrated to a greater extent than did cortisone alcohol in alkali-burned eyes after drop instillation, as well as in normal eyes after subconjunctival injection. With abraded eyes hydrocortisone alcohol penetrated almost five times as much as did the alcohols of cortisone and fludrocortisone, both of which penetrated to about the same extent. With normal eyes the penetration of cortisone alcohol was about twice that of the alcohols of hydrocortisone and fludrocortisone.

*Effect of Removal of Epithelium upon Penetration of Steroids.*—The results show that removal of the epithelium permitted a marked increase in the penetration of hydrocortisone alcohol and cortisone acetate, with a distinct decrease in the penetration of cortisone alcohol. No appreciable change in penetration was observed with hydrocortisone acetate or with fludrocortisone acetate and alcohol forms.

*Effect of Alkali Burn upon Penetration of Steroids.*—It can be seen that with eyes in which inflammation was experimentally induced by an alkali burn the penetration of cortisone acetate, hydrocortisone alcohol, and fludrocortisone alcohol markedly increased in each case, while that of cortisone alcohol and hydrocortisone acetate only slightly improved, and that of fludrocortisone acetate slightly decreased.

## COMMENT

Despite the extensive use of the corticosteroids cortisone and hydrocortisone, and, more recently, of fludrocortisone (9α-fluorohydrocortisone), in ocular therapeutics, no definite correlation exists between chemical structure and therapeutic efficiency. On the contrary, the experiences to date suggest an empirical approach to the local use of corticosteroids in the treatment of ocular infections. This situation is due, in part, to the relatively small number of different corticosteroids available for use in clinical ophthalmology and, perhaps in larger part, to the lack of knowledge concerning the physical and chemical properties of the substances in contact with the ocular tissues.

This investigation was initiated in an attempt to determine whether any correlation exists between the penetration of the corticosteroids into the anterior chamber of rabbit eyes and their chemical structure, and the therapeutic efficacy of the local use of these drugs in clinical ophthalmology. It is evident from the results that the rate of penetration of the particular corticosteroid into the aqueous humor of the anterior chamber is dependent upon the specific experimental condition and that no definite correlation can be established between rate of penetration and chemical structure of the steroids. It is assumed that the local application of the corticosteroid has no significant effect upon the level of the corticosteroids normally present in the aqueous humor, and that the measured increase is due to the penetration of the applied substance. It is significant, however, that in 8 of the 12 experiments (Fig. 1) comparing the relative effectiveness of penetration of the alcohol and acetate forms, the alcohol form of the steroid was markedly superior; in two cases the penetrations of the two forms were about the same, while in only one case did the acetate penetrate to a greater extent than the alcohol (cortisone, given subconjunctivally). This observation may, perhaps, account for the relative superiority of the free-alcohol form of hydrocortisone over the acetate in the treatment of intraocular lesions, as noted by Hogan and co-workers[2] and Gordon and co-workers.[3] In this connection, it is interesting that Hamashige and Potts[6] observed in penetration studies using C-14-ring-labeled cortisone acetate on pentobarbital (Nembutal)-anesthetized rabbits that the acetate was converted partly into the free-

alcohol form and partly into the free alcohol of hydrocortisone in the cornea and in the aqueous humor. On the basis of this transformation they suggested that the hydrocortisone alcohol may be the actual therapeutic agent. These authors also observed that hydrocortisone alcohol did not penetrate as well as did cortisone acetate, suggesting that corneal penetration of corticosteroids is dependent upon lipoid solubility (the acetate is more soluble in fat solvents than the corresponding alcohol), as noted by Cogan and Hirsch[7] and Swan.[8] Our results, on the contrary, indicate that the alcohol forms of the steroids tested penetrate, on the whole, to a greater extent than do the corresponding acetates. This apparently greater ease of penetration of the free-alcohol form of hydrocortisone suggests that it may disappear more rapidly from the intraocular tissues and fluids. Time studies along these lines have not been completed. However, in order to achieve a rapid penetration and prolonged therapeusis, it may be desirable to use clinically a combination of the free-alcohol and acetate forms of hydrocortisone locally.

At the present time the only advantage of fludrocortisone would appear to lie in the fact that clinically it is active at a lower concentration than the two compounds. This might result in a regimen of treatment less expensive to the patient.


## SUMMARY

The rates of penetration of cortisone, hydrocortisone, and fludrocortisone (9α-fluorohydrocortisone) into the aqueous humor of normal rabbit eyes and eyes whose corneas were burned with alkali and eyes whose epithelia were removed were measured after subconjunctival or drop instillation.

No definite correlation could be drawn between rate of penetration and chemical structure of the corticosteroid.

In general, the free-alcohol form of the steroid penetrated to a greater extent than the corresponding acetate.

The ease of penetration of each of the locally applied steroids does not appear to be a major factor in determining its anti-inflammatory potency.


## REFERENCES


1. McDonald, P. R.; Leopold, I. H.; Vogel, A. W., and Mulberger, R. D.: Hydrocortisone, Compound F, in Ophthalmology, A. M. A. Arch. Ophth. **49**:400, 1953.

2. Hogan, M. J.; Thygeson, P., and Kimura, A. S.: Uses and Abuses of Adrenal Steroids and Corticotropin, Tr. Am. Ophth. Soc. **52**:145, 1954; A. M. A. Arch. Ophth. **53**:165, 1955.

3. Gordon, D. M.: Ocular Therapy with the Topical Application of Hydrocortisone, Ann. New York Acad. Sc. **61**:549, 1955.

4. Weimar, V. L., and Leopold, I. H.: Intraocular Penetration of Local Hydrocortisone and Cortisone, A. M. A. Arch. Ophth. **52**:769, 1954.

5. Green, H.; Sawyer, J. L., and Leopold, I. H.: Investigation of Corticosteroids in the Aqueous Humor of Normal Animal Eyes: II. Further Observations, Am. J. Ophth. **39**:871, 1955.

6. Hamashige, S., and Potts, A. M.: Penetration of Cortisone and Hydrocortisone into the Ocular Structures, Am. J. Ophth., to be published.

7. Cogan, D. G., and Hirsch, E. O.: The Cornea: VII. Permeability to Weak Electrolytes, Arch. Ophth. **32**:276, 1944.

8. Swan, K. C., and White, N. G.: Corneal Permeability: I. Factors Affecting Penetration of Drugs into the Cornea, Am. J. Ophth. **25**:1043, 1942.

# Some Effects of Ultrasonic Energy on the Rabbit Eye

CHRISTOPHER H. MOORE, M.D.
J. F. HERRICK, Ph.D.
and
THEODORE G. MARTENS, M.D., Rochester, Minn.

Considerable controversy and confusion appear in the literature regarding the effects of ultrasound on the eye because the exact conditions of the experimental procedures are not clearly defined and understood. Fischer [1] has reviewed the biologic action of ultrasound, classifying the effects as thermal, mechanical, and chemical. Begui [2] considered that knowledge of the physical characteristics of the different parts of the eye as they affect the propagation of ultrasonic waves would be useful. He measured the density and the viscosity in the refractive parts of the eye (aqueous, lens, and vitreous), together with the velocity of the ultrasonic waves and their absorption coefficient.

The purpose of our investigation was to observe the effects of ultrasonic energy on the structures of the eye of the rabbit. Observations were made on intact as well as on enucleated eyes. Different outputs of energy and various durations of exposure to ultrasound were used. Ophthalmoscopic studies of the eyes were made before and after irradiation. After enucleation, the eyes were prepared for histologic examination and were studied microscopically.

Received for publication Sept. 6, 1955.

A portion of this paper was read at the meeting of the Midwestern Section of the Association for Research in Ophthalmology, Rochester, Minn., April 30, 1955.

Abridgment of thesis submitted by Dr. Moore to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Ophthalmology.

Fellow in Ophthalmology, Mayo Foundation (Dr. Moore). Section of Biophysics (Dr. Herrick) and Section of Ophthalmology (Dr. Martens), Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

## METHODS AND APPARATUS

Albino rabbits averaging about 3 kg. in weight were chosen for this study. Preliminary experiments were performed on enucleated eyes to develop a satisfactory technique for the later experiments in vivo and to confirm certain observations of previous investigators. These eyes were obtained immediately after the animals were killed; eyes that were not used at once were kept in an isotonic solution of sodium chloride at 5 C until used, which was not more than 20 hours later. The excised eye was held in a movable eye holder of glass, which facilitated accurate positioning of the cornea 12.5 cm. from the sound head in the ultrasonic field. The apparatus was suspended in a stainless-steel tank, with mineral oil as a coupling agent. Before each experiment, the oil was degassed for approximately a half-hour by means of ultrasound.

An ultrasonic generator (sonostat), manufactured by the Siemens Reiniger Werke, was used. Its frequency was 800 kc, and the maximal output of power was approximately 50 watts. The radiating surface area of the sound head was 10 sq. cm. The transducer was constantly cooled during operation by circulating water. A measurement of the total output of the ultrasonic generator was obtained through the use of a Siemens sonotest.

Initial observations revealed the difficulty of accurately positioning the eye in the ultrasonic field so that the cornea and lens received the maximal amount of energy. Slight errors in positioning resulted in eccentrically placed gross changes in the cornea and lens. This situation was corrected by plotting the transverse vertical and transverse horizontal patterns, as well as the longitudinal pattern, of the ultrasonic field, using the thermistor as a probe (Fig. 1). Before each

experiment, the exact position for maximal intensity of sound was determined along both the vertical and the horizontal transverse axis. The probe was then removed and replaced by the eye with great care. Early experiments used techniques in which the sound head was both stationary and moving, but stationary irradiation was found preferable. All eyes used in these studies were carefully examined grossly and ophthalmoscopically before irradiation and were found to be normal.

Thirty enucleated eyes were irradiated for varying periods and at various intensities. Observations were made continuously during the period of irradiation, after which the eyes were examined grossly. The cornea and the lens were carefully removed, and both were examined under a microdissector. The state of the vitreous was noted, although no attempt was made to measure the viscosity.

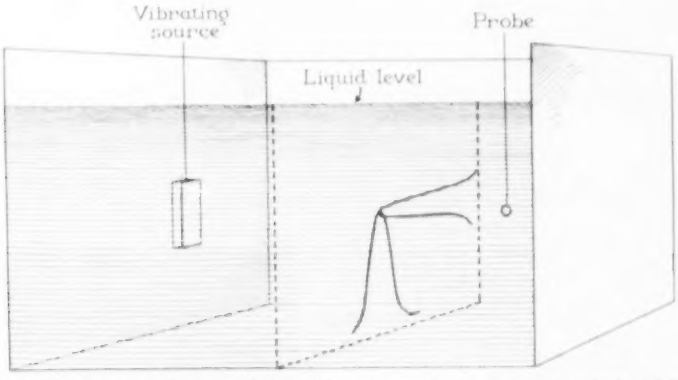



Fig. 1.—Diagram illustrating use of thermistor as a probe to plot the vertical and horizontal patterns of the ultrasonic field.

The temperature of the vitreous of 12 enucleated eyes was measured before, during, and after exposure to ultrasound for one hour. Accurate temperatures were recorded galvanometrically by means of a copper-constantan thermocouple mounted in a 20-gauge hypodermic needle that was inserted into the vitreous through the posterior pole of the eye. The deflections from the galvanometer were read directly from the scale. These were recorded continuously on moving photographic film in the final experiments. Temperatures during the cooling period following ultrasonic irradiation were observed for 30 minutes. Two experiments were performed to determine the temperature of the vitreous of the intact eye before and after exposure to ultrasound. Each rabbit was anesthetized by means of pentobarbital sodium given intravenously in a dose of 1 mg. per kilogram of body weight. Two nonabsorbable surgical (silk) sutures were used to retract the lids, and the thermocouple was inserted into the vitreous through a small scleral incision just posterior to the temporal aspect of the corneal limbus and held in position by a purse-string suture.

Two additional experiments were done in order to determine whether increased temperature alone is sufficient to cause opacities in the refractive media of the eye. A thermocouple was inserted into the vitreous posteriorly, and the enucleated eye was immersed in a bath containing an isotonic solution of sodium chloride; the temperature of this bath was controlled by an immersed heater. When the thermocouple readings became stabilized, the temperature of the bath was gradually increased and then maintained at 60 to 60.8 C for 12 minutes. By means of a thermistor placed in the vitreous, a comparison was made of the temperature observed during ultrasonic irradiation of the eye of a dead rabbit with that previously observed when the animal was alive.

Finally, experiments were performed in vivo on 12 rabbits, divided into three groups. Each rabbit received one ultrasonic irradiation to one eye, the other eye acting as a normal control. The stationary technique was used, with mineral oil as a coupling agent. The total output of the generator was 10 watts for each group. The time of irradiation for one group of four rabbits was 2½ minutes, and those for the other two groups were 5 and 10 minutes, respectively. The irradiated eye was removed from one rabbit in each of these groups at intervals of 24 hours, 6 weeks, and 12 weeks after irradiation. The fourth rabbit in each group was kept as a stand-by in case of unexpected death of one of the others in the group.

It was necessary to introduce a shielding device in order to avoid excessive heating of the bony orbit and destruction of the soft tissues adjacent to the bone (Fig. 2). The shielding device contained pockets of air for preventing transmission of sound to the extraocular region.

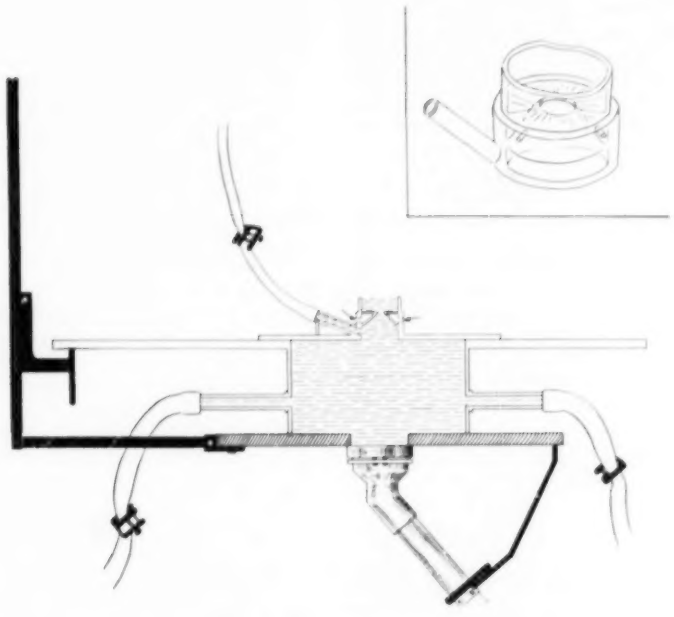


Fig. 2.—An adapter for coupling the ultrasonic energy to the cornea. Acoustic shielding of the bony orbit was accomplished by the air space, as indicated.

The material for histologic study was preserved in formalin. Paraffin sections were made and stained with hematoxylin and eosin.

## RESULTS

*Enucleated Eyes.*—The appearance of tiny bubbles of gas during irradiation generally tended to be several minutes earlier when greater intensities of ultrasound were used. These bubbles usually appeared slowly at first on the surface of the cornea and then more rapidly; finally, they appeared from the posterior surface of the eyeball (Fig. 3). They gradually subsided. Examination by means of a microdissector after irradiation of some eyes disclosed tiny bubbles of gas embedded in the epithelial surface of the cornea and the capsule of the lens. These were most apparent after use of greater intensities of ultrasound.

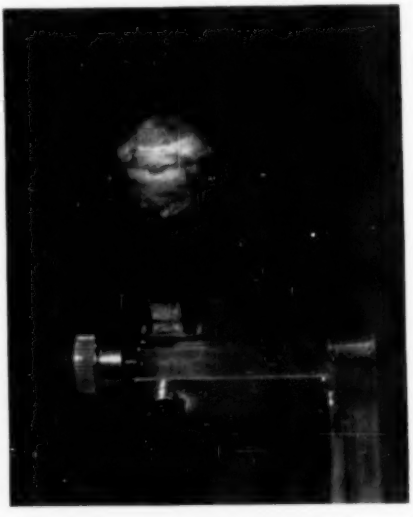


Fig. 3.—Appearance of bubbles of gas on the eyeball as the result of exposure to ultrasound.

Clouding of the cornea and the formation of dense opacities also occurred earlier after the higher doses. Observations after irradiation were limited in many eyes to gross changes because of the unsatisfactory view obtained through the cloudy cornea with an ophthalmoscope. Use of the hand slit lamp was not found practical and was discontinued. Corneal opacities were diffuse and,

as in classification of the lens opacities, were graded arbitrarily. Again, it was apparent that the densest corneal opacities were obtained after use of higher doses. Lens opacities were generally diffuse and cortical; increase in the density of the posterior transverse suture line was noted in most cases. The eyes exposed to the higher doses showed the densest opacities in the anterior cortex, while the reverse was the case in those exposed to smaller doses. The densest lens opacities also were noted with the greater doses of ultrasound. The globe in all cases felt warm and firm, suggesting an increase in intraocular tension and temperature.

In a few instances, brown discoloration of the posterior portion of the globe was present, indicating a burn. This was usually seen adjacent to attachments of muscle, and the muscle appeared to have been cooked. The vitreous was clear and of normal consistency in all eyes.

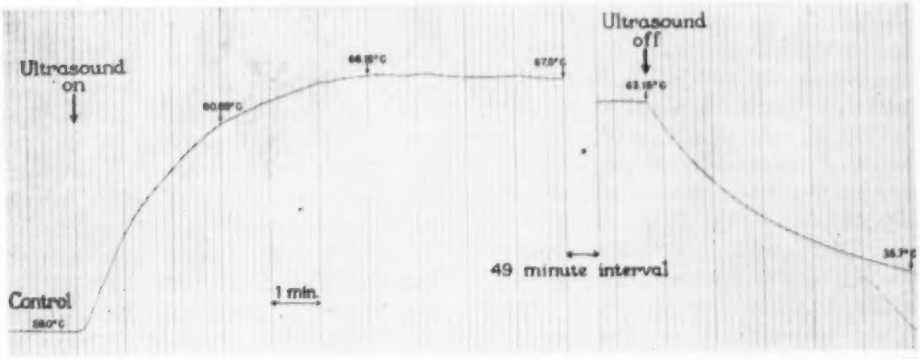
It may be concluded that the greatest effects were produced when the enucleated eyes were irradiated with the larger doses. When the greatest damage was done to the cornea, the effect on the lens was greatest in the anterior cortex; with less severe damage to the cornea, the effect on the lens was greatest in the posterior cortex. This result may be explained on the basis that with greater damage to the cornea there might be greater absorption of ultrasound, with the consequence that less ultrasonic energy reaches the posterior cortex. In some cases, however, the lens opacities were uniformly diffuse.

Exposure of enucleated eyes to ultrasound resulted in a rapid increase in the temperature of the vitreous, from a control level of 28 C to a value of 60.65 C within three minutes and to a maximum of 68.15 C within another three minutes (Fig. 4). A gradual decrease in temperature occurred when the ultrasound was turned off.

*Gross Findings in Eyes Irradiated in Vivo.*—Minimal Dose of Ultrasound: This dose consisted of 10 watts (total output) for two and a half minutes. The area of the radiating surface was 10 sq. cm., with the intensity of sound considered to be 1 watt per square centimeter. Immediately after such irradiation, the conjunctivae of the eyes so exposed were moderately injected, and pronounced miosis was present (Fig. 5*a*). The corneas were clear, and the fundi appeared normal. By the following day, a corneal opacity was present in each eye, preventing a satisfactory view of the fundus. Slight circumcorneal injection and mild hyperemia of the iris were noted in one eye. The lenses in all eyes were clear. Gradually the corneal opacities cleared and the injection subsided. The lenses remained clear, and the fundi remained normal.

Moderate Dose of Ultrasound: This dose consisted of 10 watts (total output) for five minutes. Immediately after irradiation, the

Fig. 4.—Changes in temperature of the vitreous before, during, and after ultrasonic irradiation of the enucleated eye.



corneas of the eyes so irradiated were hazy and the fundus was not seen clearly. The pupils were miotic and the conjunctivae were injected and chemotic. Numerous tiny punctate areas of hemorrhage were present on both lids in one rabbit, and within 24 hours these lids appeared burned (Fig. 5*b*). The following day the corneas of two eyes had become more opaque but the cornea of one eye had cleared sufficiently to allow examination of the fundus, which was normal. Injection and chemosis had increased, and severe circumcorneal injection was present in one eye. A few tiny corneal blood vessels appeared in this rabbit in one quadrant one week after irradiation; although most of the corneal opacity had

Fig. 5.—Effects immediately following in vivo exposure of eyes to ultrasound. (*a*) Exposure was of 10 watts' total output for two and a half minutes. Note miosis, conjunctival injection, and central corneal opacity. (*b*) Exposure was of 10 watts' output for five minutes. Note conjunctival injection, chemosis, corneal opacity, and burned lids.

cleared at the time of enucleation, six weeks after irradiation, a small opacity remained in the area of corneal vascularization. The cornea of the third rabbit was clear 1 week after irradiation, and the lens and fundus appeared normal until enucleation, 12 weeks later. The vitreous was normal in all eyes.

Maximal Dose of Ultrasound: This consisted of 10 watts (total output) for 10 minutes. An almost diffuse corneal opacity was present in all eyes of this group immediately after irradiation, obscuring a satisfactory view of the fundus. The pupils were miotic, and severe injection and chemosis of the conjunctivae were noted. The lids were edematous and congested; numerous tiny punctate areas of hemorrhage were seen in both lids of one rabbit. The corneas were completely opaque on the following day, and the congestion of the conjunctivae had increased. The lids were burned. Two weeks after irradiation, portions of the lids of two rabbits were necrotic, and a thick yellow discharge was present in the affected eyes. The palpebral apertures were extremely narrowed, and the corneas remained densely opaque. In one rabbit three weeks after irradiation, the swelling of the lids and periorbital tissue obscured any view of the cornea and the eye felt stony because of increased intraocular tension. Six weeks after irradiation, the necrotic lower lid of this animal sloughed, exposing the bony inferior orbital margin. The tension in this eye gradually subsided. At the time of enucleation, 12 weeks after irradiation, a small, shrunken globe rotated superiorly was all that could be palpated, and the cornea was not seen. When this eye was prepared for sectioning, the cornea appeared densely opaque and yellow and had new vessels on its surface. The lens was white and occupied most of the anterior chamber and vitreous cavity. The vitreous was firm and gray in appearance. The eye could not be seen or palpated in one rabbit three weeks after irradiation, and profuse thick yellow discharge was present. When enucleation was done, six weeks after irradiation, the globe was shrunken and the cornea was yellow, opaque, and ragged, containing new vessels on its surface. When this eye was prepared for sectioning, a dense, white, opaque lens was seen, with numerous thick, irregular strands radiating through the vitreous cavity to the posterior pole.

*In Vivo Development of Lens Opacities.*—The development of opacity of the lens was observed during the course of in vivo studies. The occurrence of such opacities will be described as noted in two eyes.

The first eye was exposed to an ultrasonic dose of 20 watts (total output) for two and a half minutes. Immediately after irradiation, the lids were edematous and the conjunctiva

was injected and chemotic. The inferior half of the cornea was gray and opaque. The retina appeared normal, as viewed through the relatively clear superior portion of the cornea. The pupil was miotic. Three days later the cornea was diffusely opaque. Four weeks after irradiation the palpebral fissure was greatly narrowed. The cornea remained diffusely opaque, and many new vessels were noted superiorly extending from the limbus to the cornea. The cornea had become clearer six weeks after irradiation, and an irregular, dense lens opacity was noted for the first time at the posterior pole slightly nasal to the center of the lens. This opacity appeared as two small oval-shaped clusters of black dots separated by a relatively clear central zone. It did not extend anteriorly into the nucleus but remained localized to the posterior cortex. During the next three months the lens opacity became slightly larger and then less diffuse and less dense. A small dense round irregular corneal opacity remained inferiorly, and in this region the cornea was well vascularized. A faint localized haziness was all that remained of the lens opacity three and a half months after irradiation. The corneal opacity and vessels remained unchanged.

The second eye with an opacity of the lens was exposed to an ultrasonic dose of 10 watts (total output) for five minutes. Immediately after irradiation, pronounced injection of the conjunctival vessels was noted, with a diffuse corneal haze that prevented a clear view of the fundus. The cornea was completely opaque by the next day, and there were severe chemosis and increased injection of the conjunctival vessels. The margins of the lids became red and thickened, and the palpebral aperture was narrowed. Tiny new blood vessels extending to the cornea from the limbus superiorly were first noted 14 days later. The cornea gradually became clearer. A lens opacity was first observed at the posterior pole 25 days after irradiation. This opacity was irregular and wing-shaped, each wing being oval and joined superiorly by a band. It consisted of many small black dots and was granular in appearance, with a slightly clearer central portion. During the next three months, the opacity became a little more diffuse and less dense; it remained localized to the posterior cortex and gradually decreased, until a few fine, dust-like granules were all that remained at the end of three months. The corneal opacity almost completely cleared, and the fundus was normal. The corneal vessels were still faintly seen. Hyphema was noted 13 weeks after irradiation; this obscured the fundus, but it gradually cleared within the following week.

*Histologic Findings.*—Both immediate and delayed effects were noted histologically; again, these changes varied with the duration of exposure to ultrasound.

In general, the effects were most pronounced in the anterior segment of the eye. The immediate changes were congestion of the anterior segment with edema of the cornea, destruction of epithelial cells, formation of spongy regions in the deeper stroma, and irregularities of individual cells, including the formation of vacuoles and changes in size and shape of the nuclei. Great variation was seen in the staining affinity of the cells. The anterior chamber contained a loose, delicate fibrin network, in which eosinophiles and erythrocytes were present. The capsule of the lens was displaced in some regions, and the subcapsular epithelium showed irregularities in the nuclei and clear vacuoles in the cytoplasm. Spongy zones and irregular staining were noted, mostly in the posterior cortex. Erythrocytes were present in the vitreous.

The delayed effects were largely a process of repair. The cornea became epithelized. A slight increase was noted in the number of mitotic figures in the basal epithelial cells, and there was evidence of cellular migration, and even keratinization of the epithelium in one instance. The congestion and cellular infiltration of the anterior segment were less after 12 weeks. The severe damage to the eyes exposed to maximal doses of ultrasound was striking; perforation of the globe was noted in one animal.

The delayed effects in this group resulted in endophthalmitis in all irradiated eyes.

COMMENT

During our preliminary experiments on the enucleated eyes, considerable difficulty was experienced in reproducing the results of ultrasonic irradiation. Careful plotting of the pattern of the field of irradiation, both axial and perpendicular to the vibrating surface (the sound head), and repeated checking of the ultrasonic equipment before each experiment enabled us to obtain reproducible results. Accurate positioning of the part to be irradiated was most important.

This study shows that ultrasound has a destructive effect on the eye of the rabbit. The degree of destruction caused by any given dose of ultrasound is not predictable, however, owing to the great variability of reaction of different tissues to ultrasound. It was noted that the degree of formation of bubbles and the severity of the corneal and lens opacities were greatest when the largest doses of ultrasound were used. Limited significance was attached to the changes produced in the enucleated eyes because of the unphysiologic conditions present during this part of the study. However, the experimental study using enucleated eyes determined the technique that was followed when the eyes were irradiated in vivo.

Direct heating of the enucleated eye by immersion in warm isotonic solution of sodium chloride produced no evidence of formation of bubbles, and the opacities in the cornea and lens were definitely diffuse; this picture is in contrast to the less uniform changes and the presence of bubbles of gas seen after ultrasonic irradiation.

Preliminary studies performed for the standardization of technique in vivo again stressed the variability of results and the severe and destructive effects of larger doses of ultrasound. In a few instances severe damage to the eyelids and periorbital tissue resulted from failure to direct the energy correctly. Complete occlusion of the palpebral fissures due to injury and subsequent scarring was noted in two rabbits. Bender and associates [3] have shown that ultrasound causes appreciable heating of muscle and subcutaneous tissue and a selective heating of bone that is not possessed by any other form of diathermy. Our studies have confirmed the observation that the soft tissues adjacent to bone may be severely damaged by ultrasound, owing to the multiplication of energy due to reflection from the bone. When ultrasonic energy passes from one medium to another having a different acoustic impedance, it may be scattered and reflected at this interface. The fact that burns were observed in some animals which received doses similar to those given to animals that did not experience burns again indicates the variability of response of tissues to ultrasound.

The vitreous of all the eyes irradiated in vivo was normal, except for one eye that received a maximal dose of ultrasound and in which the vitreous was gray and firm. This is in contrast to the observations of a number of European workers who have described irreversible liquefaction of the vitreous. The considerable and rapid increase in temperature of the vitreous that occurred during ultrasonic irradiation must be attributed to the absorption of ultrasonic energy.

The immediate effects of ultrasound on the eye in vivo varied with the duration of exposure. The minimal dose of ultrasound produced moderate injection of the conjunctival vessels, whereas the cornea and lens were clear on the first day. By the following day, however, corneal opacities were present in all eyes so treated. The intermediate dose of ultrasound produced more injection and chemosis of the conjunctivae, and the corneas were hazy immediately after irradiation. The maximal dose caused the greatest degree of conjunctival injection and chemosis and the densest corneal opacities. The lids were congested and edematous, and small punctate zones of hemorrhage were present in the lids in one instance. All pupils were miotic after ultrasonic irradiation and were usually in mid-dilatation within 24 hours.

The delayed effects of ultrasound likewise varied with the duration of exposure. The eyes exposed to minimal doses of ultrasound had no injection and clear media at the end of 6 and 12 weeks, respectively. With the intermediate dose, the corneal opacities had entirely cleared in one eye and had almost cleared in another, in which some corneal vascularization had developed. The delayed effects were greatest when the maximal dose was used. The lids were severely burned and were necrotic in places. The palpebral apertures were extremely narrowed, obscuring any view of the cornea. A thick profuse yellow discharge was present. Vascularization of the cornea was noted when the eyes were enucleated subsequently. During the actual irradiation, observation of the eyes was difficult, due to visual obstruction caused by the ultrasonic apparatus, but a tendency to blepharospasm and retraction of the eyeball was apparent in most eyes.

The predominantly eosinophilic cellular reaction to ultrasound is not easily explained. It is somewhat like a foreign-body reaction and may be associated with destruction of protein. The spongy zones described in the stroma of the cornea and in the cortex of the lens are predominant in the posterior portions of these structures, suggesting that the greater destruction in this region is due to structural heating caused by the differences in acoustic impedance between the cornea and the aqueous and between the lens and the vitreous. The changes in the nucleus and cytoplasm of individual cells, including the presence of clear vacuoles, were seen mainly in the basal epithelial cells, the endothelial cells, and the subcapsular epithelial cells. It is emphasized, again, that these structures present definite interphases to the passage of ultrasound; thus, depending on the amount of acoustic impedance produced, structural heating may be in part responsible for these changes. We cannot rule out the possibility that some of these effects, such as the formation of vacuoles and of clear and spongy zones, may be due to cavitation or simple degassing processes. Tremendous energy may be liberated during the phenomenon of cavitation; to what degree the observed destruction of tissue may be caused by cavitation in this series of experiments has not been investigated. A study of changes caused by cavitation includes the use of various frequencies of ultrasound and of high-pressure chambers.

The dosage of ultrasound used in these experiments was within the range of accepted therapy (approximately 1 watt per square centimeter) and was determined by the effects produced in the preliminary studies. The stationary technique, using continuous energy, was preferred because of the necessity of procuring more accurate positioning of the part exposed in the ultrasonic field. Also, we wished to avoid damage to lids and adjacent structures. Depending on the dose, ultrasound is known to produce various changes in the skin and superficial tissues, including hyperemia, edema, petechiae, and necrosis. Our observations have confirmed this occurrence. The edema may be explained on the basis of increased capillary permeability. Dittmar [1] has shown that ultrasound may have an irritative effect on nerve fibers in blood vessels, so that moderate doses produce local vasodilatation and more intense doses cause local vasoconstriction. We have noted the congestion of the lids and eye with moderate doses and the necrosis of the lids with maximal doses. The normal control eye in each rabbit was regularly examined, and no abnormalities were noted.

## SUMMARY AND CONCLUSIONS

A study was made of the effects of various doses of ultrasound on the eyes of rabbits; both enucleated eyes and normally situated eyes were used. Since some type of damage was observed in all the irradiated eyes of these rabbits, and since the minimal dose of ultrasound used was a single exposure of 10 watts for two and a half minutes, it appears likely that the minimal dose that will cause damage to the eye is even less than the minimal dose used in this study

when the stationary technique for applying ultrasound is employed.

Accurate positioning of the part to be exposed in the ultrasonic field is essential if reproducible results are to be obtained. Although the doses recommended by other workers for therapy are between 1 and 2 watts per square centimeter with the stationary technique, such doses are considered to be excessive in the light of this investigation. Ultrasound has a destructive effect on the eye of the rabbit, and it is considered, of course, that ultrasonic therapy should not be applied to the human eye under the experimental conditions used in these studies. The amount of ultrasonic energy absorbed depends on the physical properties of the eye, the positioning of the eye in the ultrasonic field, and the frequency and intensity of the ultrasonic source.

The difficulty of dosage and the control of distribution would appear to constitute major problems in the therapeutic use of ultrasound.

Considerable and rapid increase in the temperature of the vitreous occurs during ultrasonic irradiation, and this must be attributed to the absorption of ultrasonic energy. No liquefaction of the vitreous was observed during this study, in contrast to the findings of some other investigators. Cataracts developed in the posterior pole in the eyes of two living rabbits irradiated with ultrasound; these opacities subsequently disappeared.

Further studies suggested by this investigation include a comparison of the effects of ultrasound on the eye of the rabbit in vivo when an isotonic solution of sodium chloride is used instead of mineral oil as the coupling medium, and determination of the composition of the gas liberated from the tissues during irradiation with ultrasound.

## REFERENCES

1. Fischer, E.: Basic Biological Effects of Ultrasonic Energy, Am. J. Phys. Med. **33**:174-188 (June) 1954.

2. Begui, Z. E.: Acoustic Properties of the Refractive Media of the Eye, J. Acoust. Soc. America **26**:365-368 (May) 1954.

3. Bender, L. F.; Herrick, J. F., and Krusen, F. H.: Temperatures Produced in Bone by Various Methods Used in Ultrasonic Therapy: An Experimental Study, Arch. Phys. Med. **34**:424-433 (July) 1953.

4. Dittmar, Carl: Über die Wirkung von Ultraschallwellen auf tierische Tumoren, Strahlentherapie **78**:217-230, 1948-1949.

## ADDITIONAL REFERENCES

Donn, A.: Ultrasonic Wave Liquefaction of Vitreous Humor in Living Rabbits, A. M. A. Arch. Ophth. **53**:215-223 (Feb.) 1955.

Grün, P.; Funder, W., and Wyt, L.: Über die Wirkung des Ultraschalles auf den Glaskörper und auf die Linse, Klin. Monatsbl. Augenh. **116**: 358-367, 1950.

Haptén, K., and Palm, E.: Effect of Ultrasonic Vibrations on the Living Rabbit Eye, Acta ophth. **32**:227-234, 1954.

Kleifeld, O., and Fuchs, R.: Über die Wirkung des Ultraschalles auf das Tierauge und die Linse, Ultraschall in Med. **7**:9-20 (March) 1954.

Lavine, O.; Langenstrass, K. H.; Bowyer, C. M.; Fox, F. E.; Griffing, V., and Thaler, W.: Effects of Ultrasonic Waves on the Refractive Media of the Eye, A. M. A. Arch. Ophth. **47**:204-219 (Feb.) 1952.

Schwab, F.; Wyt, L., and Binder, R.: Zur Frage der Ultraschallwirkung auf die Hornhautnerven, Klin. Monatsbl. Augenh. **122**:693-704, 1953.

Zeiss, Erich: Über Linseveränderungen an herausgenommenen Rinderlinsen durch Ultraschalleinwirkung, von Graefes Arch. Ophth. **139**:301-322, 1938.

# Action of Alkalies on the Corneal Stroma

W. MORTON GRANT, M.D.
and
HAROLD L. KERN, Sc.D., Boston

Among the commonest and most devastating chemical injuries of the eye are those caused by strong alkalies, such as calcium hydroxide, sodium hydroxide, and potassium hydroxide. Contact with these substances may render the corneal stroma opaque, and vision may be lost. In combating the effects of these alkalies, copious emergency irrigation with water is important for decontamination, but thereafter the treatment available is nonspecific, save in the instance of the most superficial opacification from lime, which may be eliminated by means of sodium ethylenediaminetetraacetate or other solubilizing agent for calcific deposits.[1] General anti-inflammatory measures, including the application of cortisone and hydrocortisone, appear to be beneficial; but, unfortunately, the mode of action of alkalies on the corneal stroma is at present too poorly understood to provide a logical basis for devising specific chemical antidotes. Owing to the complexity of the chemistry involved, there is unlikely to be any speedy solution to this problem. In the work to be described in this report certain elementary aspects of the reaction of alkalies with the stroma have been examined, with the aim of making possible future improvements in means of treatment.

Previous work on alkali burns of the eye has been comprehensively reviewed by Hughes[2] in 1946, and since that time little has been published that is germane to the present study. In his review Hughes expressed the interesting opinion that in alkali burns the severity of the lesion is less dependent upon the character of the cation than on the concentration of the alkali, the duration of the exposure, and the pH of the solution. In this connection Friedenwald, Hughes, and Herrmann[3] established that injury to the corneal stroma increased sharply when the alkalinity of a solution containing sodium ions was increased above pH 11.5, but apparently no actual experimental comparison has been made with alkalies other than sodium hydroxide.

Other significant observations concerning the mechanism of injury have been related to alteration of the corneal mucoid. As reported by Hughes,[2] determination of hexoseamine and metachromatic staining before and after a single exposure to sodium hy- several days, although opacification of the corneal mucoid gradually decreased during several days, although opacification of the cornea was almost immediate. The mechanism and significance of this loss of hexoseamine have not been determined. Somewhat to the contrary, Haurowitz and Braun* have reported that calcium hydroxide (lime) causes an insolubilization of the mucoid within the cornea rather than a loss of the mucoid.

Received for publication Sept. 26, 1955.

Howe Laboratory of Ophthalmology, Harvard Medical School, and Massachusetts Eye and Ear Infirmary.

This investigation was supported by a research grant (B-103) from the National Institute of Neurological Diseases and Blindness, of the National Institutes of Health, U. S. Public Health Service.

* References 4 and 5.

It has been observed by several clinical investigators that exposure of the cornea to lime in vivo leads to formation of calcareous deposits in the cornea,[2] but in rabbits the calcium content of the cornea has been reported to return to normal four weeks after exposure, despite which the cornea remained opaque.[5]

Several of the factors mentioned in the preceding paragraphs appeared to deserve further investigation in the interest of establishing a firmer basis for future work. This has been the objective of experiments to be reported here: (1) Comparison has been made of the conditions conducive to stromal injury by a variety of alkalies in order to ascertain experimentally whether the pH or the character of the cation governs injuriousness to the cornea; (2) the fate of the cation, calcium in particular, has been investigated in vivo and in vitro, and the relationship to corneal opacity has been examined, and (3) the reported insolubilization of mucoid in the cornea by lime has been reexamined. Only those findings which may be of ophthalmologic interest are presented in this report; details of chemical methods and observations concerning the chemical nature of binding of cations by the corneal stroma may be found in a separate biochemical report.†

## EXPERIMENTAL STUDY

### Determination of Chemical Conditions for Injury of the Cornea by Alkalies

The objective was to establish whether the threshold of pH for opacification of the corneal stroma, which has been reported as approximately pH 11.5 for sodium hydroxide,[3] is common to different alkalies irrespective of the nature of their cation. This was ascertained by dropping test solutions on the eyes of rabbits for 15 minutes at room temperature after scraping off the corneal epithelium. In Table 1 are presented the results of exposures to a series of equimolar solutions (0.023 M) of alkalies which were adjusted to pH 11 and to pH 12 with hydrochloric acid, or, in certain cases, with aminoacetic acid or arginine. In order to assess the influence of varying alkalinity, it was necessary to restrict the selection of cations to those which we have found essentially noninjurious to the corneal stroma at neutrality, thereby eliminating from consideration certain cations which we have found to be innately toxic, such as the long-chain quaternary ammonium compounds, certain dyes, beryllium, scandium, yttrium, and the lanthanons (rare earths).

Table 1.—*Response of Corneas of Rabbits Exposed to 0.023 M Solutions of Alkalies for Fifteen Minutes with the Epithelium Removed*

| | | |
|---|---|---|
| A. | At pH 11 and below: Slight and reversible injury after exposure to the following alkalies: | |
| | Sodium hydroxide | Tetramethylammonium hydroxide |
| | Sodium hydroxide—aminoacetic acid buffer | Tetraethylammonium hydroxide |
| | Sodium hydroxide—arginine buffer | Trimethylamine |
| | Potassium hydroxide | Triethylamine |
| | Calcium hydroxide | Tributylamine |
| | Barium hydroxide | Diethanolamine |
| | Strontium hydroxide | Piperidine |
| | Ammonium hydroxide | |
| B. | At pH 12: Severe injury with opacity after exposure to the following alkalies: | |
| | Sodium hydroxide | Barium hydroxide |
| | Sodium hydroxide—aminoacetic acid buffer | Strontium hydroxide |
| | Sodium hydroxide—arginine buffer | Ammonium hydroxide |
| | Potassium hydroxide | Tetramethylammonium hydroxide |
| | Calcium hydroxide | Tetraethylammonium hydroxide |

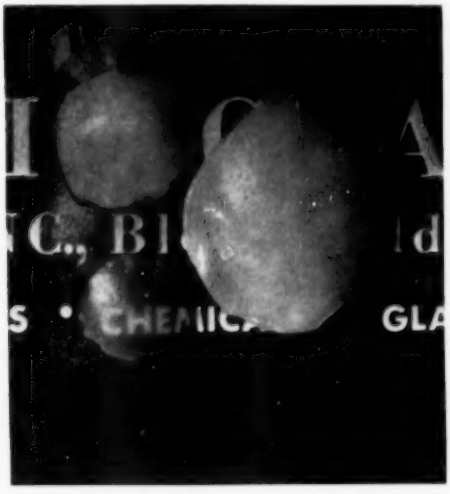
Certain of the bases tested at pH 11 are missing from the list of those tested at pH 12, but this is only because these particular substances dissociated insufficiently to reach pH 12 at 0.023 M concentration, and therefore could not be tested at pH 12 without addition of some other cation. No significant difference was observed between buffered and unbuffered solutions.

In an additional set of experiments the concentration of certain of the inorganic cations listed in Table 1 was increased sev-

† Kern, H. L., and Grant, W. M., paper in preparation.

eral fold by adding the respective chloride salts while the alkalinity was maintained at pH 11; no increase in injury was observed. It is apparent from these observations and the results listed in Table 1 that injury of the denuded corneal stroma by alkalies is in general governed by the pH rather than by the nature or concentration of the cation.

Incidental to these studies, variations were observed in the types of opacity which were induced by different alkalies, and variations have also been observed in different animal species. Visual comparisons of excised beef, rabbit, and human corneas after exposure to a series of alkalies at pH 12 confirmed observations which have previously been reported in the literature that the alkaline earths (calcium, barium, and strontium) cause an opacity in beef and rabbit corneas which is whiter than that caused by sodium and potassium.[3] However, in human corneas we have found the effect of calcium hydroxide to differ in two respects from that found in animal eyes. The opacity induced in human corneas by lime was distinctly less white than the opacity induced in beef and rabbit corneas. This difference, which is shown by the corneas in the accompanying Figure, was not related to corneal thickness, since human cornea is intermediate in thickness between beef and rabbit cornea. The other difference in response of human and animal corneas to lime has become apparent in biomicroscopic study of patients shortly after accidental exposure. In human corneas a lamina of granular gray opacity forms approximately at the level of Bowman's membrane, but in animal eyes we have not found this apparently selective localization. Possibly this difference is attributable to an absence of Bowman's membrane in the subprimates. The special whiteness of opacity caused by alkaline earth cations in animal eyes had not yet been satisfactorily explained.



Comparison of the opacification induced by lime in corneas of different species. Excised cattle cornea (on the right), rabbit cornea (upper left), and human cornea (lower left) developed these different degrees of opacity after 15 minutes in saturated calcium hydroxide solution. Opacification was not related to the corneal thickness, since human cornea was thicker, yet less opaque, than rabbit cornea.

### Investigation of the Chemical Reaction of Alkalies with the Corneal Stroma

It has occasionally been postulated that upon exposure of the cornea to alkalies a metal proteinate is formed,‡ but this proposed reaction has scarcely been studied at all. In the present work measurements have been made of the extent to which various cations enter into combination with, or are "bound" by, the corneal stroma, and information has been obtained on the components and chemical groups in the cornea which are involved in this reaction. The methods employed and results obtained are to be found more fully described in a separate publication. In brief, in those studies corneas were exposed to solutions of alkalies under various conditions and the amount of cation which was bound was determined by chemical analysis after the unreacted portion of the solution had been removed by pressing in a hydraulic press. Examination of the relationship of binding of cations and the pH of the solution revealed a steep

‡ References 2 and 6.

increase in binding in the range from pH 10.5 to 12, corresponding approximately to the range of steep increase in injuriousness to the cornea which was shown in the preceding section of the present report. Comparison of the corneal stroma with purified collagen, with sclera, and with corneal stroma from which mucoid had been extracted gave evidence that in near-neutral solutions the cations are bound almost exclusively by the mucoid of the cornea, but that with elevation of pH into the injurious range the increased binding of cations is accomplished by the collagen. The number of ionized acidic groups, such as carboxyl, and the net charge on the stromal proteins appear to be major factors governing the binding of cations. This was ascertained in experiments in which the binding of cations was measured before and after various groups were blocked by methylation, by ammonolysis following methylation, by acetylation, and by reaction with formaldehyde and nitrous acid.§

The avidity with which the cornea binds various cations from solution was evaluated by comparing the binding of cations individually and from mixtures. In essence, it has been found that at pH 12 the concentration of cations bound within the stroma is approximately 10 times the concentration of cations in the surrounding solution, owing presumably to the number of reactive anionic groups in the tissue. The cornea binds approximately equimolar amounts of various cations from pure solution, but in solutions of mixed cationic composition the cornea has an approximately tenfold greater affinity for the alkaline-earth cations, calcium, barium, and strontium, than for sodium and potassium.

Combination of alkalies with both mucoid and collagen is rapid, but reversal by dilution is relatively slow. Hydroxyl ions are consumed in the reaction at high pH and are regenerated when the reaction is allowed to reverse at lower pH. The process envisaged may be exemplified by the following equation:

$$^{+}H_3N\cdot Cornea\cdot COO^{-} + NaOH \underset{\text{Water}}{\overset{\text{Alkali}}{\rightleftharpoons}} H_2N\cdot Cornea\cdot COONa + H_2O$$

The slow reversibility of this reaction and the gradual regeneration of hydroxyl ions presumably account for the common observation that, following exposure of the eye to alkalies, neutrality is regained slowly despite copious irrigation with water.‖

The relationship of injury and the binding of cations by the corneal stroma is not known. The binding of sodium, potassium, calcium, barium, and strontium by the mucoid of the cornea near neutrality appears to be innocuous, and there is only the coincidence of increased binding by collagen with increased injuriousness in the range of pH 11 to 12 to suggest a causative relationship. Two principal considerations which remain to be elucidated are whether the presence of cation in association with collagen is in itself deleterious to the cornea, or whether the reaction of cations with collagen promotes some other reaction, such as the displacement of mucoprotein. Some information bearing on these points has been obtained in the following experiments.

### Fate of Calcium in Rabbit Eyes Exposed to Lime

The corneas of anesthetized rabbits were mechanically denuded of epithelium and were then irrigated for 15 minutes with a saturated solution of calcium hydroxide (0.023 M, pH 12.4), followed by water for 15 minutes. This exposure to lime caused complete whitening of the cornea and led to necrosis and eventual perforation of the eyes of most of the rabbits which were kept for observation. For determination of the rate of disappearance of calcium, sample corneas were removed and analyzed at various intervals after exposure. The results are listed in Table 2.

The normal calcium content of rabbit corneas was found to be 0.2-0.6 mg. per gram,

§ Kern, H. L., and Grant, W. M., paper in preparation.

‖ References 2 and 6.

and the elevated calcium content of the corneas which had been exposed to lime generally dropped back to the normal range within a day following exposure. The corneas were dense white immediately following exposure to lime, and this opacity did not appear to change despite the subsequent decrease in calcium content. However, after the first day an interesting change occurred, which may not have a counterpart in human eyes. In the rabbit eyes there was commonly, but not invariably, a rapid secondary rise in calcium content to levels even greater than those observed immediately following exposure to lime, and this was associated with the appearance in the cornea of hard white plaques, whiter than the surrounding cornea. The phosphate content of the cornea was found to increase considerably at the same time. It seems highly probable that these plaques of secondary calcification in the rabbit owe their whiteness and opacity to the deposition of material containing calcium phosphate. The mechanism for the secondary, endogenous calcification is not known, but it may well be a rather nonspecific response in rabbits, for we have observed the same sort of calcareous plaque formation to follow injury of rabbit eyes with a number of noncalcific chemicals (e. g., yttrium and several of the rare earths). Irrigation of rabbit corneas with a neutral solution of edathamil sodium (sodium ethylenediaminetetraacetate) to remove calcium rapidly following exposure to lime minimized the subsequent development of the plaques.

TABLE 2.—*Calcium Content of Corneas in Rabbits at Various Intervals After Exposure to Saturated Solution of Lime*

| Time Following Exposure | Calcium Content, Mg. per Gm. Wet Wt. |
|---|---|
| 15 min | 1.8, 2.2, 2.3 |
| 75 min | 2.3, 2.5 |
| 2 hr | 0.9, 1.4 |
| 6 hr | 1.2, 1.4 |
| 22 hr | 0.3, 0.3, 0.3, 0.4, 1.2 |
| 2 days | 0.2, 1.7, 5.6 |
| 4 days | 0.2, 4.5 |
| 7 days | 4.2, 5.4, >6 |

Incidental to the foregoing experiments we have corroborated the fact that the calcium content of the cornea may be greatly raised at neutrality without causing opacification.¶ When the denuded corneas of rabbits were irrigated with 10% calcium chloride solution for 15 minutes, the corneas remained clear and subsequently recovered well from the exposure. The total calcium content was elevated to the same level as by irrigation with saturated lime. However, the proportion bound by the cornea was not ascertained in this experiment. In rabbit eyes return to the normal level after exposure of the denuded corneas to 10% calcium chloride for 15 minutes required only two to three hours and was, accordingly, appreciably more rapid than after exposure to calcium hydroxide. The calcium content of the aqueous humor after exposure of the eyes of rabbits to 10% solution of calcium chloride rose as high as 4 mg. per milliliter (compared with 0.1 mg. per milliliter in normal eyes), but following exposure to saturated calcium hydroxide for 15 minutes no rise was found in the calcium content of the aqueous humor. The elevation of calcium concentration in the aqueous humor caused miosis, but no significant injury. From the therapeutic standpoint there seems, therefore, to be no reason to try to remove calcium from the anterior chamber by paracentesis of the cornea following lime burns.

Since an abnormally high concentration of calcium has been found to persist in the cornea for some time following exposure to calcium hydroxide, consideration has been given to whether the degree of injury might be influenced by the length of time the excess calcium remains. The slow reversibility of the reaction of calcium hydroxide with the cornea, suggested by the observations on rabbit eyes described in previous paragraphs, has been corroborated in experiments on excised cattle corneas.# It was

¶ References 2 and 5.

# Kern, H. L., and Grant, W. M., paper in preparation.

found that the calcium bound by these corneas during exposure to calcium hydroxide (for one hour) could be only gradually extracted by washing with a large volume of water during several days. An attempt to accelerate the release of calcium and to evaluate the influence of this treatment on corneal injury has been made experimentally. Edathamil sodium in approximately neutral (pH 7 to 8) solutions has been utilized for irrigation of lime-exposed corneas in rabbits with the aim of removing calcium as rapidly as possible. This substance has low toxicity to the cornea under the conditions selected. It is a highly efficient chelating agent for calcium, and might be expected rapidly to eliminate free calcium and possibly to promote the release of the bound form. By measurements on rabbit cornea in vivo and on human cornea in vitro, it has been determined that during the first hour after exposure to lime the total calcium content of the cornea can be more rapidly reduced by irrigation with edathamil sodium than by irrigation with water. Experimentally, to test the effect on lime burns, 23 rabbits have been given symmetrical exposure of the corneas to saturated solution of calcium hydroxide, and in each rabbit one eye has been treated by irrigation with a solution of edathamil sodium, and the contralateral eye has been irrigated equally with water as a control. The conditions of exposure to saturated lime varied from a maximum of 15 minutes' irrigation of the whole eye after removal of the corneal epithelium, to a minimum of 15 minutes' localized application to a central disc of intact cornea by means of a 5-mm.-diameter glass suction cup. The concentration of edathamil sodium employed was varied from 0.01 to 0.1 M, and the duration of irrigation from 15 to 45 minutes. During subsequent observation for as long as seven months it was found that treatment with edathamil sodium did not greatly benefit the lime-burned rabbit eyes under any of these conditions. However, in 6 out of 23 rabbits the corneas treated with edathamil sodium ultimately appeared slightly less opaque than the control eyes, and in no case was the treated eye worse than the control. The treatment with edathamil sodium did not cause permanent damage to normal eyes, although at 0.1 M concentration the solution induced transient stromal edema, considerably more than did similar treatment with water. At 0.01 M concentration the solution caused no appreciable irritation.

Experimental results with edathamil sodium correspond essentially to our clinical experiences with this substance in treatment of lime burns of human corneas. When opacification has extended deeper than approximately the level of Bowman's membrane, irrigation with edathamil sodium has had no notable effect. Only the superficial calcific opacities which resemble those of endogenous band keratopathy respond noticeably to treatment with edathamil sodium.[1] Clinically, edathamil sodium has been found to have practical application in removal of these superficial calcific opacities [1]; also, for emergency decontamination of eyes exposed to solid particles of lime, irrigation with edathamil sodium aids in release of particles which otherwise tend to adhere tenaciously to the conjunctiva and cornea.*

Since edathamil sodium was found to have little influence on deep opacities induced in the corneal stroma by lime, a second form of treatment, irrigation with dilute hydrochloric acid, was evaluated. Beneficial effect has been claimed for this treatment in human eyes, and in our chemical studies we have observed that acid is effective in extracting calcium from lime-exposed cattle corneas in vitro. To investigate the effect on corneal opacification from lime, the same experimental procedure was employed as described in the evaluation of edathamil sodium in rabbit eyes, except that hydrochloric acid at pH 1 and pH 2 was substituted for the edathamil sodium. The treatment with acid caused some immediate temporary clearing of the lime-induced opacity of the rabbit corneas, but subsequently the opacification

* Potts, A. M.: Personal communication to the authors. Gaines, S. R., and School, R. E.: Personal communication to the authors.

of acid-treated corneas became gradually worse than that of the controls. The acid treatment on normal corneas caused much less damage than it did on corneas which had been exposed to lime. It was concluded that attempted rapid removal of calcium from the cornea by means of dilute hydrochloric acid has more detrimental than beneficial effect.

The failure to reduce stromal opacity in lime-burned eyes by treatments which utilize edathamil sodium or hydrochloric acid for rapid removal of calcium constitutes additional evidence that the opacity is not dependent upon the continued presence of calcium. Furthermore, these results indicate that in the initial reaction of the cornea with lime some change is wrought in the cornea itself, and that this is not reversed by removal of lime or by lowering the pH.

### Influence of Alkalies on Corneal Mucoid

The binding of cations by the corneal stroma in the region of pH 12 appears to be associated in some way with injury of the corneal stroma which is not reversed by subsequent elimination of the cation. No evidence has been found of permanent alteration of the collagen, but some evidence has been presented in the literature for change in the mucoid portion of the stroma.† We have reexamined the status of the mucoid by repeating the experiments of Haurowitz and Braun,[5] and by evaluating in other ways the extractibility of mucoid following exposure of the cornea to alkalies.

Haurowitz and Braun ‡ came to the conclusion that lime (calcium hydroxide) caused a precipitation of mucoid within the cornea, and that this precipitate was responsible for the opacity of the cornea. This precipitate they believed to consist of denatured mucoid, not a persisting combination of calcium and mucoid, because they had observed that added calcium did not remain long in the cornea even though the opacity did. Their conclusion that mucoid was precipitated in the cornea was based principally on experiments in which cattle corneas were soaked for 15 minutes in lime solution and were compared with normal corneas by the following procedures: Groups of four normal and four lime-exposed corneas were extracted for eight days with a 0.2% solution of ammonium hydroxide with daily change of the extraction fluid. Each group of corneas was then soaked for 24 hours in 10 ml. of 0.5 N hydrochloric acid at room temperature; subsequently, the acid extracts were heated for half an hour at 80 C. Next, the extracts were neutralized with 10 ml. of 0.5 N sodium hydroxide and tested for reducing sugar by adding 5 ml. of Fehling's solution and heating. Weak reduction of the Fehling solution was observed in the extract from normal corneas, but strong reduction, in that from the lime-exposed corneas. This was interpreted to mean that more mucopolysaccharide was extractible with acid from lime-exposed corneas than from normal corneas.

We have repeated the above experiment but obtained a negative Fehling's test for reducing sugar in the acid extract from both groups of corneas. Furthermore, we have found, on examining this experiment more closely, that an equal amount of mucopolysaccharide is removed from both normal and lime-exposed corneas by the ammonia extraction, and that no significant difference in residual saccharide is detectable in the acid extracts even by means of a more sensitive test than that based on Fehling's solution (the Nelson-Somogyi arsenomolybdate technique). Further, systematic variation of the time and temperature of acid hydrolysis failed to yield results like those of Haurowitz and Braun. Thus, contrary to these investigators, we found no evidence by this type of experiment to suggest that mucoid is precipitated in the cornea by lime.

Seeking further information on the influence of lime on the mucopolysaccharide of the cornea, we have examined the extractibility of this substance by gentle

† References 2, 4, and 5.

‡ References 4 and 5.

methods from normal and lime-exposed corneas. We have found that less than 5% of the mucopolysaccharide (based on ester-sulfate assay) of normal beef corneas is extractible in 24 hours by means of 0.9% solution of sodium chloride at room temperature. Utilizing this rather inefficient, yet physiologic, extractant, we have compared the rate of extraction of mucopolysaccharide from normal corneas (beef) and from corneas which had immediately previously been exposed to saturated solution of calcium hydroxide for 10 minutes. The pH of the saline solution was held close to neutrality by measurement with a glass-electrode pH meter and addition of necessary amounts of hydrochloric acid. It was found that two to three times as much acid polysaccharide was extractible from the lime-exposed corneas as from the normal controls. Investigation of the influence of the pH of the lime solution revealed that only when the initial exposure was more alkaline than pH 11 was the subsequent extraction of acid polysaccharide by isotonic saline solution significantly enhanced. This apparent liberation of a portion of the mucopolysaccharide of the cornea by the action of lime suggests some similarity to the action of sodium hydroxide, which, as mentioned in the introduction, has been observed to diminish the hexoseamine content and metachromatic staining. This phenomenon is presumably a counterpart of the observation by Woodin of dissociation of corneal mucoprotein at pH greater than 12.[7] Whether a dissociation or depolymerization of mucoprotein is related to injury of the cornea in the clinical sense remains to be determined by further experiment.

## CONCLUSIONS

In general, the severity of injury of the corneal stroma by alkalies is governed by the pH rather than by the nature of the cation. However, there are exceptions to this rule in the case of certain substances which even near neutrality are injurious to the cornea (e. g., long-chain quaternary ammonium compounds, certain dyes, beryllium, and the lanthanons); these substances will be discussed in a separate paper. The general rule applies to the reaction of the stroma alone; the epithelium may modify the result by influencing the rate of penetration of substances from the outer surface to the stroma.

Sodium, potassium, calcium, barium, and strontium are bound by the mucoid of the cornea in an innocuous manner near neutrality; but as the pH is increased, these cations are bound in increasing proportion by the collagen, particularly in the range corresponding to steep increase in injuriousness. Ionized anionic groups in the tissue are essential for binding cations, and the binding may be experimentally blocked by blocking these groups. Injury is not reversed by subsequent elimination of the cations from the cornea, and the opacity in rabbit eyes which is induced by exposure to lime persists despite return of the calcium content of the cornea to normal. Speeding removal of calcium from the stroma by irrigation with edathamil sodium (sodium ethylenediaminetetraacetate) has slight influence on the stromal opacification, although this treatment is very effective in removing calcific deposits which are superficial to the stroma in human eyes and is useful in emergency decontamination of the eyes of patients after exposure to particulate lime. Irrigation of lime-burned rabbit eyes with dilute hydrochloric acid (pH 1 and 2) results in worse injury than that from lime alone.

Reversal of the binding of cations by the stroma by means of dilution (washing the cornea with water) occurs relatively slowly and is accompanied by regeneration of hydroxyl ions; this accounts for the notorious slowness with which the eye regains neutrality following exposure to alkalies in spite of copious irrigation with water or salt solution.

No evidence was found for precipitation of mucopolysaccharide in the cornea by lime. Instead, the extractibility of the mucopolysaccharide of the cornea by 0.9% sodium chloride solution was found to be increased

twofold to threefold following brief exposure of the cornea to lime.

Further experimentation will be necessary to establish whether the binding of cations by the cornea at alkaline reaction and the release of acid mucopolysaccharide are interrelated, and whether these phenomena are related to corneal opacification.

REFERENCES

1. Grant, W. M.: A New Treatment for Calcific Corneal Opacities, A. M. A. Arch. Ophth. **48**:681-685, 1952.

2. Hughes, W. F.: Alkali Burns of the Eye, Arch. Ophth. **35**:423-449, 1946.

3. Friedenwald, J. S.; Hughes, W. F., and Herrmann, H.: Acid-Base Tolerance of the Cornea, Arch. Ophth. **31**:279-283, 1944.

4. Braun, G., and Haurowitz, F.: Experimentelle, histologische und therapeutische Versuche zur Kalkverätzung der Kornea, Klin. Monatsbl. Augenh. **70**:157-165, 1923.

5. Haurowitz, F., and Braun, G.: Zur Kalkverätzung der Kornea, Ztschr. physiol. Chem. **123**: 79-89, 1922.

6. Carpenter, C. P., and Smyth, H. F.: Chemical Burns of the Rabbit Cornea, Am. J. Ophth. **29**: 1363-1372, 1946.

7. Woodin, A. M.: The Properties of a Complex of the Mucopolysaccharide and Proteins of the Cornea, Biochem. J. **58**:51-57, 1954.

# News and Comment

## SOCIETY NEWS

**The Association for Research in Ophthalmology, Inc.**—The Mid-West Section of the Association for Research in Ophthalmology will meet at Northwestern University in Chicago on Saturday, March 17, 1956. The Chicago Ophthalmological Society will have a meeting on the following Monday, March 19, 1956, so that those who attend the Mid-West Section may also attend the Chicago Society meeting if they wish.

The Section is anxious to have a selected and varied program that will have a wide appeal to the associated sciences related to ophthalmology. The title and a short résumé of the subject matter of investigation should be sent by Oct. 21 to the President, Arlington C. Krause, M.D., 950 E. 59th St., Chicago 37.

## ANNOUNCEMENT

**Appointment of Dr. David G. Cogan.**— Dr. David G. Cogan, Director of the Howe Laboratory of Ophthalmology of the Harvard Medical School and the Massachusetts Eye and Ear Infirmary, in Boston, has been appointed to serve on the National Advisory Neurological Diseases and Blindness Council. His appointment was announced by Surgeon General Leonard A. Scheele, of the Public Health Service, U. S. Department of Health, Education, and Welfare.

Dr. Cogan, a noted investigator into the causes of blindness, has served as a consultant to the National Research Council, the Public Health Service, the World Health Organization, and other groups interested in ophthalmic disorders. With his new appointment, he becomes one of the 12 Council members who advise the Surgeon General on an important part of the research program of the National Institute of Neurological Diseases and Blindness, Bethesda, Md.

Upon recommmendations of this Council, as established by Act of Congress in 1950, the Surgeon General awards grants to scientists in hospitals, universities, and other nonfederal institutions throughout the country for the conduct of research into the neurological and sensory disorders, including cerebral palsy, multiple sclerosis, epilepsy, and diseases causing deafness and blindness.

The National Institute of Neurological Diseases and Blindness is one of seven and other nonfederal institutions throughout the country for the conduct of research branch of the Public Health Service. Each Institute conducts a research grant program aided by a National Advisory Council. The members of these Councils are leaders in science, educational, and public affairs. They meet three times yearly at Bethesda, Md.

# Clinical Notes, New Instruments and Techniques

## A NEW CONTACT LENS ELECTRODE FOR CLINICAL ELECTRORETINOGRAPHY

JERRY HART JACOBSON, M.D., New York

MUCH OF the difficulty in performing routine electroretinography has been due to the discomfort of the contact lens electrode and, to a greater degree, of the speculum recommended by Karpe.

In an effort to overcome this difficulty, the illustrated lens was devised. It is a conventional scleral type contact lens, 24 by 25 mm., with two tubular tunnels projecting from the convex surface. These are 2 mm. in diameter and 10 mm. long. One contains the silver-silver chloride electrode and the joint by which the electrode is attached to a wire lead, which connects to the input of the ERG machine. The second tunnel is hollow and is used, after the lens is in place, to fill the lens with isotonic saline in a methylcellulose solution.

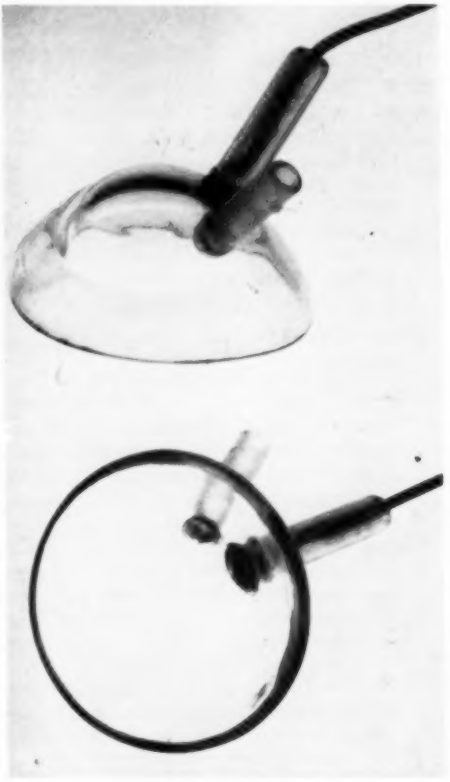
A large part of the discomfort of the test as previously performed was produced by the manipulation required to fill the lens after insertion when the lens of Karpe was used. This new lens is easily filled, after insertion, without moving it, by inserting the end of a fine dropper filled with the solution into the tunnel. The methylcellulose is far superior to the aqueous saline originally used, since it does not tend to run out of the lens, thus preventing the formation of an air bubble.

The two projections from the external surface serve to keep the lids from closing, but do not produce the discomfort and consequent squeezing of the lids that are found when a speculum is used. Over 300 ERG's have been performed with this lens, with no difficulty.

The lens is manufactured by Obrig Laboratories, of New York, and the methylcellulose was furnished by Robert R. Feinstein, of Ophthalmos Labs, North Bergen, N. J.

880 Fifth Ave. (21).

Above, external view of lens; below internal view of lens.



Received for publication Aug. 31, 1955.

From the Division of Electrophysiology, Department of Research, New York Eye and Ear Infirmary.

This study was supported by the Arnold Reuben Fight for Sight Fund of the National Council to Combat Blindness and the National Society for the Prevention of Blindness.

# Annual Reviews

## GLAUCOMA

### A Review of the Literature for 1954-1955

JOSEPH S. HAAS, M.D., Chicago

I. The Primary Glaucomas
A. Classification
B. Mechanism
1. Narrow-Angle Glaucoma
2. Wide-Angle Glaucoma
(*a*) Hypersecretion
(*b*) Aqueous Retention
(1) Trabeculum
(2) Aqueous Veins
(3) Venous Pressure
(4) The Hypothalamus
(5) Allergy
(6) The Endocrine System
(7) Miscellaneous Factors
C. Diagnosis
1. General Considerations
2. Tonometry
3. Provocative Tests
4. Tonography
5. Perimetry
6. Phasic Variations
7. Gonioscopy
8. Fluorophotometry
D. Medical Treatment of Glaucoma
1. Acetazoleamide (Diamox)
2. The Miotics
(*a*) Cholinergic Drugs
(*b*) Anticholinesterase Drugs
3. The Sympatholytic Drugs
4. Miscellaneous Drugs
E. Surgical Treatment of Glaucoma
1. General Considerations
2. Iridectomy
3. Iridencleisis
4. Trephination and Anterior Sclerectomy
5. Cyclodialysis
6. Cyclodiathermy
7. Goniotomy
8. Miscellaneous Operations
II. Congenital Glaucoma
III. Secondary Glaucoma

Recorded for publication Sept. 30, 1955.

## I. THE PRIMARY GLAUCOMAS

### A. Classification

THE EVIDENCE supporting the classification of the primary glaucomas into narrow- and open-angle glaucoma has been discussed in the preceding Annual Reviews on glaucoma. The many facets of this concept are described by Roper [1] in a discussion of the etiology and diagnosis of primary glaucoma. The literature for 1954-1955 has contained nothing of significance regarding the amplification or refinement of this concept.

### B. Mechanism

Further evidence of harmony is reflected in the writings of the proponents of the so-called mechanical and neurovascular schools of the pathogenesis of glaucoma. Sir Stewart Duke-Elder,[2] in speaking of the glaucoma symposium of the International Congress of Ophthalmology, states, "The symposium made it abundantly clear that this distinction did not in fact exist; differences in approach and in the technicalities of the language accounted for differences in view-point which were discovered to be more apparent than real."

Sugar [3] agrees that the mechanism of primary glaucoma cannot be thought of on the basis of conflicting mechanical or neurovascular mechanisms. The mechanical mechanism is activated by neurovascular stimuli, while the neurovascular mechanisms often require some mechanical changes to be effective.

Thus, it would seem that in general a unanimity of opinion has arisen regarding the classification and clinical course of the primary glaucomas. This calm, however, has not produced any diminution of effort toward the eventual understanding of the pathogenesis of glaucoma, as is demonstrated by the excellence of the experimental work which has appeared.

Kinsey [4] justifies his conclusion that both secretion and diffusion are simultaneously active in the formation of the aqueous. Measurements were made of the rate of accumulation of sodium and thiocyanate in the posterior and anterior chambers of the rabbit eye. The data for the entrance of sodium to the posterior chamber were found to fit a curve derived from a secretory hypothesis, whereas those for the thiocyanate were found to fit a curve from a diffusion hypothesis. By application of an elaboration of a theory of aqueous humor dynamics to the determinations, the rate of flow out of the anterior chamber would appear to be between 1.7% and 2% per minute of the volume of the anterior chamber.

Bárány [5] has improved the paraaminohippuric acid method for estimating rate of flow of aqueous humor and found it to be 1.1% per minute of the volume of the anterior chamber. This discrepancy is discussed in Kinsey's [4] paper.

An obviously stimulating result of the above experiment is reported by Bárány and Wirth,[6] who found a very marked decrease in the rate of flow of the aqueous as an occasional result of paracentesis of the contralateral eye in rabbits.

Evidence of some regulating mechanism for outflow is presented by de Roetth.[7] Using the tonographic method of Grant, he was able to show that hypertonic (sorbitol) solutions caused a decrease in aqueous flow, whereas hypotonic (water) solutions caused an increase in flow. This was true in both normal and glaucomatous eyes. There was, however, a startling difference in outflow between normal and glaucomatous eyes. In eyes with chronic simple glaucoma the facility of outflow did not seem to change with the above changes in inflow, whereas a compensatory alteration of outflow was noted in normal eyes. Thus, the resistance to outflow appears to be an elastic changeable factor in normal eyes.

The anatomy of this outflow mechanism receives further study from Dvorak-Theobald.[8]

1. *Narrow-Angle Glaucoma.*—The association of the critically narrow angle with the aging process is emphasized by Kornzweig,[9] who discusses angle-narrowing factors, such as the increased anteroposterior diameter of the lens, thickening of the ciliary processes, and progressive diminution in size of the pupil.

Chandler and Trotter [10] define subacute-angle-closure glaucoma as a form of glaucoma in which the elevation of tension is due solely to closure of the angle, but in which the entire angle is not closed at one time, so that the attacks of elevated tension are not as severe and intractable as in acute glaucoma. In the early stages the eye returns completely to normal between attacks, but after repeated attacks a portion or portions of the angle may remain closed by peripheral anterior synechiae, or the trabecular meshwork may be damaged by the repeated closure of the angle, or both may occur. In early cases any significant tension rise occurring under faithful miotic treatment is justification for a peripheral iridectomy.

In a concept which would be difficult to reconcile with partial closure of the angle, Posner [11] expresses belief that an iris crypt is sufficient to prevent cohesion of the iris root and trabeculum from occurring and thereby prevent an attack of narrow-angle glaucoma.

The part of emotion in producing acute glaucoma is emphasized by Diener,[12] whereas Gerloff [13] relates acute attacks to meteorological conditions. Lo [14] found that acute attacks were commonest in China during August, September, and October, the rainy season.

2. *Wide-Angle Glaucoma.*—The basic concepts of circulation of the aqueous in glaucoma are discussed simply and briefly by Posner.[15]

(*a*) Hypersecretion: Magitot,[16] a confirmed believer in the vascular etiology of all forms of glaucoma, reemphasizes his belief that the elevation of intraocular pressure is merely a symptom of glaucoma and results from engorgement of the uveal capillaries with resultant hypersecretion of fluid. He explains all the other symptoms of glau-

coma, including field defects, as being of vascular origin, but does not explain the lack of confirmation of hypersecretion provided by tonography and fluorophotometry.

(*b*) Aqueous Retention: (1) Trabeculum. Linnér [17] concludes that the outflow resistance of the corneoscleral trabeculum is increased in eyes with chronic simple glaucoma as a result of measuring the pressure drop between the anterior chamber and the canal of Schlemm. He found it to be 3.86 mm. Hg in normals, whereas it was 10.47 mm. Hg in patients with chronic simple glaucoma. He was unable to confirm Ascher's observation that the number of aqueous veins was less in eyes with chronic simple glaucoma.

A similar finding is reported by Perkins,[18] who cannulated the canal of Schlemm in monkey eyes and found the pressure in the canal of Schlemm to be 10% less than in the anterior chamber. In histologically confirmed incisions of the trabeculum this trabecular resistance decreased remarkably, allowing flow to increase two to three times.

Weekers and Delmarcelle,[19] using a fluorescein instillation test, also report that glaucoma in most forms is due to an increased resistance to flow.

The pore size of the trabeculum has long been a debated subject. Huggert [20] injected suspensions of chromium phosphate and bacteria into the anterior chamber and collected aqueous samples from the episcleral veins. Particles of 1.5$\mu$ to 4$\mu$ passed through human trabeculae and from 1.2$\mu$ to 2.4$\mu$ through rabbit trabeculae.

Thiel [21] noted clumps of vitreous cellular material in the aqueous of glaucomatous patients with the electromicroscope. In view of Huggert's findings, the size of these clumps would be of interest.

(2) Aqueous veins. The study of the aqueous veins by Ascher [22] has led him to the conclusion that primary glaucoma is an obstruction peripheral to the canal of Schlemm. This is at variance with the findings of Linnér,[17] who did not find a statistically significant difference in pressure across the outlets of the canal of Schlemm between normal and glaucomatous patients.

(3) Venous pressure. Boles-Carenini [23] found the venous pressure to be significantly higher during the morning in glaucomatous patients. In some cases of glaucoma he felt that the systemic venous pressure affected the aqueous outflow, and thus indirectly the intraocular pressure and the diurnal variations. This did not occur in normal persons.

Dobree [24] suggests that the venous pressure rise may be secondary to the intraocular pressure. If the intraocular pressure rises, the pressure is transmitted in the first place to the intraocular veins, and hence the resistance to the flow of blood through the eye is raised. A compensatory rise in arterial pressure will result, with possible widening of their lumen. In absolute glaucoma the caput medusae may result because the arteries cannot overcome the intraocular pressure and therefore the blood is shunted into the superficial veins.

(4) The hypothalamus. Von Sallmann,[25] found an area in the dorsal hypothalamus that, when electrically stimulated, resulted in elevations or falls of intraocular pressure which were isolated events and apparently were in no way connected with changes in systemic blood pressure or in the activity of the extraocular muscles. It was felt that this response was vascular in nature. No evidence of a large center could be found, for even slight movement of the electrode would cause alterations in response, and frequently involve the extraocular muscles or systemic blood pressure.

Kaneda,[26] in a similar experiment, found the intraocular pressure changes proportional to the systemic blood pressure changes.

Indirect evidence of hypothalamic control is suggested by Stepanik,[27] who found an inverse relationship between the intraocular pressure of eight glaucomatous patients and their eosinophile count. Since he assumes that the eosinophile level is controlled by the hypothalamus, he concludes that the intraocular pressure is too.

Lebedinskaia [28] studied the functional condition of the cortex in 45 glaucomatous patients by the speech-motor method of Ivanon-

Smolinsky and found that over half of the patients gave an abnormal response.

(5) Allergy. A case of acute congestive glaucoma is reported by Wiseman and Moore [29] in which attacks were precipitated by orange juice or peas and were absent when these were eliminated.

The diet records of 62 chronic glaucoma patients were calculated for calories and eight nutrients by Maslansky,[30] and no evidence of deficiency could be found.

(6) The endocrine system. Schmerl and Steinberg * have isolated two pituitary hormones from the spinal fluid of men and rabbits. One, named hyperpiesin, was found to act upon parasympathetic centers, producing vascular dilation of ocular vessels and a consequent increase in tension. Miopiesin influenced the sympathetic centers, with a resultant vascular contraction and a decrease in tension. Apparently, the anterior pituitary secretes hyperpiesin. The hormone is then modified quantitatively according to the demands of the organism by the posterior pituitary tissue. Hyperpiesin is acted upon by some catalytic substance, probably an enzyme, and a part of the hormone is converted to miopiesin. A physiological balance is established thereby and maintained as long as normal conditions exist.

When the injection of hyperpiesin raised the intraocular pressure more than 10 mm. Hg in rabbits, congestive signs appeared.

Ambrosio [33] felt that in 12 men with chronic glaucoma he could demonstrate a deficiency of testicular hormone.

(7) Miscellaneous factors. Urrets Zavalia[34] suggests that the resistance to outflow in chronic glaucoma is explained by various changes in the angle, such as diffuse sclerosis or hyaline degeneration, or by increase in the intrascleral venous pressure. All of these factors are secondary to a sclerosis of the capillary network in the anterior uvea. A similar sclerosis of the capillary network of the circle of Haller and in the retinal vascular tree may be the cause of the lacunar degeneration of the optic nerve and the alterations of the visual field.

Brand's [35] work would support this view, for he has shown that in a population of 119 glaucoma patients 12 out of 44 deaths were the result of cerebral hemorrhage. This is twice as high an incidence of apoplexy as in nonglaucomatous aged hypertensive persons.

Further evidence that glaucoma is associated with a general vascular disease is shown by Sokolowski,[36] who found impaired hearing in 58% of 40 cases of glaucoma and diplacusis in 30%. A similar finding was reported by ten Doesschate and Landsberg.[37]

The hereditary nature of familial glaucoma was studied by Desvignes and Chardin [38] in 16 families and found to be dominant, with 50% of the members in the first generation and 25% of the members in the second generation affected. The phenomenon of anticipation was common. In nonfamilial glaucoma the subsequent occurrence of glaucoma was no greater than normal. Penzani [39] traced glaucoma directly through four generations of one family.

Constitutionally, Funder [40] believes that glaucoma is more likely to develop in the pyknic type.

Huerkamp and Zieglitz [41] report that the ozone concentration of the air was not correlatable with the ocular tension of glaucomatous persons. Cristini,[42] however, felt that the oxygen uptake of the uvea is greater in glaucomatous patients, suggesting that in the glaucomatous eye there may be a slowing of the circulation, facilitating the liberation and diffusion of $O^2$ from the vessels into the tissues.

3. *Low-Tension Glaucoma.*—Alajmo and Simonelli [43] discuss three cases, diagnosed as glaucoma, in which the condition was due to pituitary adenoma in one and to optic arachnoiditis in the second; in the third the etiology could not be established. Bailbe [44] presents a case of embolism of the left central retinal artery occurring in a patient with thrombosis of the internal carotid artery on the same side, and Comberg,[45] a case of a 65-year-old man with bilateral glaucomatous

* References 31 and 32.

excavations in which all provocative tests were normal and the tension was never above 30 mm. Hg.

Most of the above cases cannot be considered as instances of true low-tension glaucoma but are included here to point out the importance of a careful differential diagnosis.

C. Diagnosis

1. *General Considerations.*—Foote [46] found that 13% of the blindness in Arkansas, Indiana, Kansas, Missouri, New Hampshire, and New York was due to glaucoma. In Iceland, 60% of the blindness is due to glaucoma, and Björnsson [47] feels that this high figure is due to self-neglect.

In Cleveland, tensions were taken in 12,000 cases in one day, and of these 1.87% had glaucoma. Wolpaw and Sherman [48] feel that it would be more practical to teach tonometry to the general physician.

Iris atrophy occurring in chronic glaucoma is discussed by Alearts,[49] who concludes that it is a vascular phenomenon. It always starts in the superior temporal quadrant and proceeds toward the inferior nasal quadrant.

Sengupta [50] believes that the neovascularization of the veins near the disc in chronic simple glaucoma is probably a shunt, due to partial obstruction at arteriovenous crossings.

The Maxwell spot (an entopic phenomenon caused by a local nonuniform distribution of the chromatic receptors in the fovea) and the Haidinger brushes (an entopic phenomenon due to the absorption of polarized light in the doubly refracting substance of Henle's fibers) are unreliable tests for the diagnosis of glaucoma, according to Schmidt.[51]

2. *Tonometry.*—Zeller and Christensen [52] and Gunderson [53] believe that routine tonometry as a part of every general physical examination would prevent much unnecessary visual loss.

Weekers and associates [54] checked the ocular tension in 300 normal patients and found that a tension higher than 25 mm. Hg was pathologic. Suda, Inamochi, and Ikuta [55] observed tensions of from 12 to 25 mm. Hg in 95% of 3174 normal eyes. The standard error of tonometry in humans was calculated at ±0.37 scale unit by Rohrschneider and Kuechle.[56] For rabbits it was ±0.75 scale unit.

An editorial [57] referring to the new calibration scale for Schiøtz, Gradle-Schiøtz, and McLean tonometers also states that intraocular pressures higher than 25 mg. on the new scale are rarely encountered in normal eyes. This new scale is published again in this article, and also in the *British Journal of Ophthalmology.*[58]

The four methods of calibration of tonometers are discussed by Jackson,[59] who feels that a detailed physical examination of the tonometers is the most practical method.

Posner [60] briefly reviews the mechanics of tonometry, using the Schiøtz type of instrument and, in a paper with Mamelock,[61] tells of his experiences with Wiegersma's [62] elastometer. This is a very light-weight ballistometric instrument, designed principally for the determination of ocular rigidity. Posner feels that this instrument measures only the elasticity of the cornea and has no clinical value as a tonometer.

Methods for sterilization of the Schiøtz type tonometer are described by Dreisler,[63] who flames the foot plate with an alcohol burner, and by Rosner,[64] who has devised a stand utilizing ultraviolet-radiation-ozone exposure.

3. *Provocative Tests.*—Leydhecker has written extensively of the provocative tests. In a discussion of their reliability,[65] the various tests were evaluated on patients with ocular tensions below 30 mm. The Vasculat (butyl sympatol) or tolazoline (Priscoline) test was the most reliable in patients with open-angle glaucoma, giving 55%-70% results. The tolazoline test is discussed in a separate paper [66] and consists of the subconjunctival injection of this vasodilator. The water-drinking test provides one-third positive results and should be administered prior to the tolazoline test.

Using the homatropine provocative test,[67] Leydhecker found that 78 eyes with wide-angle glaucoma did not show an abnormal increase in tension, whereas in 25 eyes af-

flicted with narrow-angle glaucoma the increase in tension reached pathologic zones. Gonioscopy showed that the angle of the anterior chamber was constantly blocked when a positive result occurred.

In another paper, the caffeine test [68] was described as very unreliable in glaucoma, giving only 15% positive results in eyes with tensions below 30 mm. Hg.

Finally, the mean rise to be considered as suggestive [69] in the caffeine test is 6 mm. Hg, and a rise of 9 mm. is pathologic. For the water-drinking test a rise of 8 mm. Hg is suggestive and a rise of 10 mm. Hg is pathologic; for the homatropine test, 8 and 12 mm.; for the lability test, 9 and 11 mm.; for the Vasculat test, 11 and 15 mm., and for the tolazoline test, 11 and 14 mm. Hg, respectively.

Studying the effect of the water-drinking test systemically, Campbell and associates [70] found that diuresis in the glaucomatous patient with respect to volume of urine, specific gravity, and secretion was the same as among normal subjects. The blood sodium fell at the point of maximum rise in intraocular pressure but not proportionally to the rise. The blood sodium showed a higher initial level and wider variation during the test in the glaucomatous patients.

Two unusual patients whose tension became elevated during reading or sewing and whose angles became obliterated at the time the pressure was elevated are discussed by Higgitt and Smith.[71] Surprisingly, the tension could be controlled by either miotics or mydriatics, and the darkroom and water-drinking tests were negative. It is suggested that during accommodation a rotation of the ciliary body occurred about the scleral spur and that this caused an apposition of the root of iris to the corneoscleral trabeculum.

Del Río Cabañas and Cadeñas [72] did not feel that Kleinert's compensation maximum test was very helpful in the diagnosis of early glaucoma.

Caselli [73] describes the Findeisen test, which consists of a comparison of the systolic arterial pressures in the upright and in the horizontal position plus a comparison of the pulse rate when the neck is flexed so that the chin touches the sternum. A fall of 15 mm. in blood pressure or a slowing down of eight or more heart beats is considered positive. Of 58 glaucomatous patients examined with Findeisen's test, 80% were found to show a positive result.

Pau [74] injected propadrine (norephedrine) intravenously and found a greater rise in tension in glaucomatous than in normal subjects.

4. *Tonography.*—Grant [75] has developed techniques for making tonographic measurements in enucleated eyes. With these studies he has demonstrated that the scleral rigidity in rabbits decreases spontaneously during the first hour or two after death. He has also calibrated the electronic tonometer and found that it gives results in satisfactory agreement with the mechanical Schiøtz tonometer.

Of perhaps more interest to the clinician is the finding of a similar value for facility of outflow in enucleated eyes and in the eyes of patients, suggesting that a stable structure, rather than some function of the general circulatory system or nervous system, is responsible for this resistance.

Stepanik [76] suggests that tonography for the diagnosis of chronic simple glaucoma be done at the height of the diurnal curve, for the resistance to outflow was greatest at these times.

Andreani [77] found that normal subjects always gave a normal response to Baxter's compression test. In chronic glaucoma simplex 73% of the patients showed some reduced outflow, but in prodromal glaucoma only 23% showed diminished aqueous drainage.

Suda and associates [78] demonstrated that the lowering of the ocular tension after compression of the eyeball with a 50 gm. weight for 10 minutes was 75% in normal and 30% in glaucomatous eyes. In 17 cases of glaucoma normalized by miotics and in 16 cases of so-called low-tension galucoma, the lowering was 50% and 43%, respectively, on the average, suggesting that there was still a disturbance of the regulating mechanism.

5. *Perimetry.*—François and Verriest [79] describe the field changes in glaucoma. In

acute congestive glaucoma there is a concentric contraction, associated or not with nasal depression or with elongation of the poles of the blind spot. In chronic simple glaucoma and in chronic congestive glaucoma, the arcuate scotoma, depression of a nasal quadrant, juxtacecal scotoma, central defect, and cuneate defect occur, in that order of frequency.

A concentric contraction of the field for red under low (20-lux) illumination seemed to be characteristic of early glaucoma and occurred before Seidel's or Bjerrum's scotoma.[80]

Miles and Trapp[81] attempted further to refine the technique of flicker fusion fields and could not demonstrate a striking advantage of either a particular light-dark ratio or a particular target intensity.

Concluding that the glaucomatous field defects are produced by stretching of the nerve fibers at the lamina in the glaucomatous eye, Irvine[82] demonstrated a thinning of the nerve fiber layer and a reduction of ganglion cells on the temporal side of a glaucomatous eye.

6. *Phasic Variations.* — By tonographic means de Roetth[7] learned that the diurnal variations are determined by the rate of flow of aqueous.

Huerkamp[83] measured the tension curves during the night and found a steadily decreasing curve until one hour after rising, when the curve reversed and started up.

7. *Gonioscopy.*—A brief, but comprehensive, introduction to gonioscopy and a description of the examination of the vitreous and the fundus with the slit lamp by Goldmann[84] are now available.

The trabecular region can be seen at the periphery of the posterior corneal surface in almost every person by external slit-lamp examination, and Burian and associates[85] state that in about 15% of the persons examined the trabecular region ended corneaward in a more or less prominent whitish line, identified as a prominent anterior-border ring of Schwalbe. This they found was often associated with a mild to severe hypoplasia of the anterior stromal layers of the iris and other congenital anomalies, such as corectopia, polycoria, etc., but it was not causally related to glaucoma. Allen and associates[86] feel that these rings are the result of excessive laying down of mesodermal tissue in embryonic and fetal eyes.

Further observations of the angle in patients with anterior-segment inflammations by Kravitz[87] revealed the presence of adhesions, synechiae, organized exudates, pigment, and capillaries.

Grant and Chandler[88] describe a surgical contact lens in which a continuous stream of saline is injected, and a technique for gonio-photography is described by Goodstein and colleagues.[89]

8. *Fluorophotometry.* — A study of the permeability of the blood-aqueous barrier was made by Weinstein,[90] and the chronic simple glaucoma patients showed a normal permeability. In acute glaucoma, during an attack the permeability was at the upper limit of normal, but after the attack the permeability was essentially increased.

An electrical control assembly for the slit-lamp determination of concentrations of fluorescein is described by Askovitz.[91]

### D. MEDICAL TREATMENT OF GLAUCOMA

Three reviews of the treatment of glaucoma have appeared this year. Thiel[92] divides his discussion into three parts. In the first he discusses the local treatment of glaucoma with the miotics; in the second, the uses of ergotamine, barbiturates, morphine, and Rauwolfia compounds to depress the vegetative centers of the hypothalamus, and, finally, the ganglion-blocking drugs.

Knighton[93] emphasizes that open-angle glaucoma cannot be considered controlled unless there is no field progression, and McBain[94] discusses the time-honored advantages of pilocarpine. Sugar[95] describes the virtues of the social worker in maintaining a glaucoma clinic.

1. *Acetazoleamide* (Diamox).—The import of acetazoleamide in the field of ophthalmology is unquestioned, but the mechanism by which it diminishes aqueous formation is still controversial. Acetazoleamide is a carbonic anhydrase inhibitor. The consensus is that acetazoleamide in-

hibits this enzyme, resulting in a diminution of secretion. Furthermore, Kinsey has demonstrated a 15% excess of bicarbonate in the anterior chamber as compared with the plasma, and an even greater excess (42%) in the posterior chamber fluids, of the rabbit eye. He postulates that bicarbonate may play a pilot role in the formation of the aqueous humor. Thus, it has been further assumed that the inhibition of carbonic anhydrase may interfere with the production or availability of bicarbonate and thus inhibit the formation of aqueous.

Friedenwald [96] supports this hypothesis and describes two distinct mechanisms by which it could occur. The effect of sodium bicarbonate and ammonium chloride on these mechanisms is contemplated. Becker [97] summarizes the tonographic evidence supporting this theory. To rule out the effects of diuresis, he emphasizes the tension-lowering effect of acetazoleamide in nephrectomized animals. Vogelius and Brun [98] have also demonstrated this result. As additional support, Becker mentions the findings of Linnér and Friedenwald that acetazoleamide induces a delay in the appearance time of intravenously injected fluorescein into the anterior chamber.

Similar findings, plus the clinical use of acetazoleamide, are described by Breinin and Görtz.[99]

Other investigators are not in agreement with the above findings. Green [100] found that the intravenous administration of acetazoleamide caused a 75% reduction in carbonic anhydrase activity in the ciliary body and iris of rabbits in 15 minutes and a 93% inhibition in 30 minutes. In a later paper,[101] he reports that the drug was administered subconjunctivally, as well as intravenously, with complete inhibition of the carbonic anhydrase activity, but no significant lowering of the intraocular pressure was noted. He concluded that the maintenance of the intraocular pressure is not dependent upon the carbonic anhydrase activity of the uvea. Green [102] and his co-workers also demonstrated no significant change in the bicarbonate ion concentration of the anterior chamber aqueous humor after intravenous or subconjunctival administration of acetazoleamide and conclude that the carbonic anhydrase has nothing to do with the bicarbonate ion of the anterior chamber.

Finally, they report a new microspectrophotometric method for the determination of acetazoleamide in the aqueous humor.[103]

In an attempt to explain the absence of tension-lowering effect of acetazoleamide in some animals, Kinsey [104] altered the diet of his nonreacting rabbits so that it contained more sodium chloride. Approximately 90% of animals subsisting on a ration containing 0.5% sodium chloride responded positively, as compared with about 40% to 50% of the eyes of animals subsisting on a ration containing 0.2% sodium chloride. Of eyes demonstrated to be unresponsive to acetazoleamide, 95% were also made to respond by parenteral injection of the salt-retaining mineralocorticoid aldosterone.

Weinstein [105] believes that acetazoleamide functions by increasing the absorption of aqueous into the blood stream through decreasing the osmotic pressure of the blood, and Kleinert [106] believes that the drug relieves an edema at the chamber angle and so facilitates outflow.

Foss [107] used acetazoleamide locally, without effect on the intraocular pressure.

Clinically, Demers and Monfette [108] recommend the use of acetazoleamide in acute glaucoma, and Murphy [109] feels that it hastens formation of a flat anterior chamber after cataract extraction.

*2. The Miotics.—(a)* Cholinergic Drugs: 1. Pilocarpine. Posner [110] reports a case in which an elevation of tension followed the use of pilocarpine. He postulates that the miosis flattened an iris crypt and thereby allowed a complete cohesion between iris and trabeculum to occur. Leydhecker [111] also reports a patient with elevation of tension from miotics, but this case followed an iris bombé in secondary glaucoma.

2. Mintacol (diisopropyl-*p*-nitrophenol phosphate). This drug is considered more effective as a miotic than 4% pilocarpine by Bayo y Bayo and de la Peña.[112] Fisostina (furthrethonium-*p*-toluenesulfonate) is de-

scribed by Cascio [113] as a miotic with marked vasodilatory effect.

*(b)* Anticholinesterase Drugs: 1. Eustigmine. This is chemically identical with neostigmine (Prostigmin). Junghannss [114] frequently found it effective as a miotic when pilocarpine was not.

2. Isofluorophate. Retinal detachment as a result of isofluorophate therapy is reported by Westsmith and Abernathy.[115] Fibrinous iritis following treatment with pilocarpine, physostigmine, and isofluorophate together was seen by Zicha,[116] and Andreani [117] cautions against the use of isofluorophate in anatomically narrow angles because of the danger of precipitating an acute congestive attack.

3. *Sympatholytic Drugs.* — Primrose [118] found phenoxybenzamine hydrochloride (Dibenzyline), the successor to Dibenamine (*N,N*-dibenzyl-$\beta$-chloroethylamine), effective in lowering the pressure of 50% of the patients with acute glaucoma. The side-effects are marked and can be serious.

4. *Miscellaneous Drugs.* — Weekers and associates † report the tension-lowering effect of epinephrine, which they state is due to a reduction of inflow of aqueous. One instillation of a special solution lowered the ocular tension for two or three days. The drug is contraindicated in narrow-angle glaucoma.

François ‡ noted the occurrence of secondary glaucoma in seven cases of chronic uveitis and one of discission of the lens after several months of local therapy with cortisone. It tends to disappear after withdrawal of the drug. Laval and Collier [123] report two cases with a similar occurrence due to systemic steroid therapy. In a shorter study, Colombi [124] found no effect on pressure from local cortisone.

Sébas [125] feels that the female sex hormones decrease ocular tension and reports favorable results with progesterone.

McGuire [126] uses bishydroxycoumarin (Dicumarol) to combat glaucomatous field changes in patients below 60 years of age where the changes in field are moderate.

The maximal fall in intraocular pressure occurs eight minutes after retrobulbar injection of procaine and epinephrine, according to Bettini.[127] Tonographically, de Roetth [128] found the reduction in tension to be due to a reduction in aqueous inflow.

Smoking is shown by Sanna [129] to increase the tension, as well as the angioscotoma, and Bietti [130] demonstrates an increased response to the water provocative test with one or two cigarets. This may suggest that smoking is harmful to the glaucoma patient.

Schumacher [131] elicits a marked fall of intraocular pressure following the systemic intravenous injection of salicylic acid, and Sakamoto [132] prevents the rise of tension that occurs with oscillation of a rabbit with diphenhydramine (Benadryl).

### E. Surgical Treatment of Glaucoma

1. *General Considerations.*—In a long-term follow-up of patients subjected to the filtering operations, Sédan [133] concludes that operation is still an efficacious treatment for glaucoma. In 213 of 262 cases, the tension was normalized. He feels that late obliteration of the fistula may be constitutional and familial.[134]

Cataract formation occurred in 32.8% of 254 fistulizing operations, and LeGrand [135] believed that they were due to changes in the position of the lens and to modifications of the aqueous. Williamson-Noble [136] feels that absence of the chamber is contributory.

Hallerman [137] believes that the occurrence of pupillary excrescences which interfere with vision are an indication for operation.

2. *Iridectomy.* — The advantages of the peripheral iridectomy in narrow-angle glaucoma are recorded by Trotter,[138] Posner,§ and Stoentchev.[142]

Wudka and Leopold [143] produced elevations in intraocular pressure in rabbits with isofluorophate without angle closure occurring. Complete iridectomy partially prevented this rise, and they conclude that

† References 119 and 120.

‡ References 121 and 122.

§ References 139 to 141.

iridectomy possesses some mechanism, in addition to relief of iris bombé, for lowering the elevated intraocular pressure. Sbordone [144] feels the iridectomy increases the permeability of the blood-aqueous barrier.

3. *Iridencleisis.* — Mackie and Rubinstein [145] advocate the use of iridencleisis in preference to iridectomy in all cases of narrow-angle glaucoma, and Gildemyn [146] recommends it for secondary glaucoma in aphakia.

In Guenther's [147] opinion, the best site for the filtering area in iridencleisis is between Schlemm's canal and Schwalbe's ring. Stanković ‖ advocates the predissection of the bleb with subconjunctival air.

Incarceration of only a small piece of peripheral portion of the iris is done by Posner,[150] and the combined cataract extraction and iris inclusion operation gives good results for Wenaas and Stertzbach.[151]

Cristini [152] believes the iridencleisis functions because of a revascularization of the anterior uvea, whereas Caselli ¶ thinks it functions by increasing the permeability of the blood-aqueous barrier.

4. *Trephination and Anterior Sclerectomy.*—The outcome of a second filtering operation of the same type is frequently the same as the first, according to Klemens,[155] who feels that if the first operation fails, a different type should be preferred for the second eye. The low-grade iritis following sclerectomy operations is reviewed by Kalt and associates,[156] who advocate the therapeutic use of mydriatics and hydrocortisone.

To prevent adherence of the conjunctiva to the trephine opening, Roig [157] sutures a small silver tripod over the opening, and Stallard [158] seals the trephine opening with a scleral plug in cases of late restoration of the anterior chamber.

Dusseldorf [159] advocates an inferior trephination below if the first fails, and Foroni [160] prefers an inverted T-sclerectomy.

5. *Cyclodialysis.*—Kleinert [161] does not accept the theory that cyclodialysis functions by reducing the formation of aqueous. Kamel [162] successfully normalized the tension in one case of essential iris atrophy with cyclodialysis. Nano [163] performs his cyclodialysis through a trephine opening under the lateral rectus.

6. *Cyclodiathermy.* — Good results with cyclodiathermy are reported in 80% to 100% of his cases by Maeder,[164] in 50% by Bartolome,[165] and in 70% by Sokolić.[166]

Weekers [167] recommends cyclodiathermy as the operation of choice in absolute glaucoma, aphakic glaucoma, and glaucoma secondary to uveitis and as a secondary operation. Cascio [168] believes that it is of value in infantile glaucoma.

Covell [169] was unfavorably impressed with the operation and warns of the danger of sympathetic ophthalmia. Szymanski [170] prefers cycloelectrolysis.

7. *Goniotomy.*—Consistently better results are obtained in infantile glaucoma by Funder [171] with goniotomy than with DeWecker's anterior sclerectomy. Cusik # has developed a modified cyclodialysis spatula with a knife on its end, which does an inverted goniotomy combined with cyclodialysis.

8. *Miscellaneous Operations.*—The results of the posterior sclerotomy in 288 eyes, with severe retinal complications in 6%, are reported by Kleinert.[174]

### II. CONGENITAL GLAUCOMA

The pathogenesis of infantile glaucoma is reviewed by Barkan,[175] who reiterates his belief that the outflow of these eyes is blocked by a thin, shagreen-like membrane covering the trabeculum. This concept is supported by Siliato.[176]

Allen, Burian, and Braley [177] do not accept this opinion but are of the belief that infantile glaucoma is due to inadequate cleavage of the sinus of the angle.

These concepts are discussed along with the diagnosis and treatment of infantile glaucoma in a symposium presented at the American Academy of Ophthalmology and Otolaryngology in 1954.[178] It was unanimously

‖ References 148 and 149.

¶ References 153 and 154.

# References 172 and 173.

felt that the treatment of infantile glaucoma was surgical, and the best results were obtained with angle surgery, i. e., goniotomy and goniopuncture. Robertson [179] concurs in these recommendations.

Tyner [180] has obtained an exceptionally high percentage of successful results using the goniopuncture as a primary operation in far-advanced infantile glaucoma. The fact that this operation worked in many eyes with corneal diameters over 15 mm. suggests that its mechanism is different from that of goniotomy, which does not work as frequently in these large eyes.

Cramer [181] believes that surgical treatment of infantile glaucoma is mandatory, and Brockhurst [182] reports that of 59 premature infants, 56 had normal intraocular pressures.

### III. SECONDARY GLAUCOMA

Kronfeld [183] confirms the concept that glaucoma secondary to delayed restoration of the anterior chamber is due to decreased outflow. When miotics improve the tension, the outflow is increased.

Phacolytic glaucoma is due to the escape of lens fluid from a hypermature cataract, according to Flocks,[184] and should be prevented by the extraction of all mature cataracts.

Wilson [185] believes that capsular exfoliation does not usually cause glaucoma, but that in most cases the glaucoma is primary.

Five cases of concussion or contusion glaucoma are reported by Ingman [186] and Chinaglia.[187] Cohen and Chamlin [188] discuss the syndrome of uveitis with glaucoma and retrobulbar neuritis. Mattson [189] and Zewi [190] report a case of glaucomatocyclitic crises.

Two reports on essential iris atrophy are presented, one by de Ferrari [191] and one by Sivasubramaniam and Hoole.[192] Glaucoma due to a subluxated lens with a fluctuating anterior chamber is reported by Marchi,[193] and Wollin and associates [194] report glaucoma with bilateral ectopia lentis in a dwarf.

111 N. Wabash Ave.

### REFERENCES

1. Roper, K. L.: Modern Approach to Glaucoma, Am. J. Ophth. **39**:312, 1955.

2. Duke-Elder, S.: A Symposium on Glaucoma, Brit. J. Ophth. **38**:763, 1954.

3. Sugar, H. S.: The Mechanical and Neurovascular Schools in the Mechanism of Primary Glaucoma, Am. J. Ophth. **38**:645, 1954.

4. Kinsey, V. E.; Palm, E., and Cavanaugh, G. A.: Posterior and Anterior Chamber Aqueous Humor Formation, A. M. A. Arch. Ophth. **53**:330, 1955.

5. Bárány, E., and Wirth, A.: An Improved Method for Estimating Rate of Flow of Aqueous Humor in Individual Animals, Acta ophth. **32**:99, 1954.

6. Bárány E., and Wirth, A.: Consensual Inhibition of the Circulation of the Aqueous Humor in Rabbits, Acta ophth. **32**:113, 1954.

7. de Roetth, A.: Effect of Changes in Osmotic Pressure of Blood on Aqueous Humor Dynamics, A. M. A. Arch. Ophth. **52**:571, 1954.

8. Dvorak-Theobald, G.: Further Studies on the Canal of Schlemm, Am. J. Ophth. **39**:65 (April, Pt. II) 1955.

9. Kornzweig, A. L.: Physiological Effects of Age on the Visual Process, Sight-Saving Rev. **24**:130, 1954.

10. Chandler, P. A., and Trotter, R. R.: Angle-Closure Glaucoma, A. M. A. Arch. Ophth **53**:305, 1955.

11. Posner, A.: Role of Peripheral Iris Crypts in Protection from Narrow Angle Glaucoma, Eye, Ear, Nose & Throat Month. **33**:427, 1954.

12. Diener, F.: Inflammatory Glaucoma After Psychic Insults, Klin. Monatsbl. Augenh. **124**:393, 1954.

13. Gerloff, W.: Influence of Weather on Eye Diseases, Klin. Monatsbl. Augenh. **125**:61, 1954.

14. Lo, W. B.: Primary Glaucoma in Chengtu, Chinese M. J. **72**:41, 1954.

15. Posner, A.: Regulation of Intraocular Pressure in the Normal Eye and in Glaucoma, Eye, Ear, Nose & Throat Month. **34**:326, 1955.

16. Magitot, A.: Ocular Hypertension Is a Symptom and Not a Disease, Ann. ocul. **187**:1, 1954.

17. Linnér, E.: The Outflow Pressure in Normal and Glaucomatous Eyes, Acta ophth. **33**:8, 1955.

18. Perkins, E. S.: Pressure in the Canal of Schlemm, Brit. J. Ophth. **39**:215, 1955.

19. Weekers, R., and Delmarcelle, Y.: The Measurement of the Rate of Aqueous Flow in Man, Ophthalmologica **127**:373, 1954.

20. Huggert, A.: Experiments to Determine the Pore Size in the Filter of the Angle of the Anterior Chamber, Acta ophth. **32**:513, 1954.

21. Thiel, R., and Schwarz, W.: Electronicroscopic Examination of Components of the Aqueous, Klin. Monatsbl. Augenh. **125**:265, 1954.

22. Ascher, K. W.: The Aqueous Veins in Glaucoma, Boll. ocul. **33**:129, 1954.

23. Boles-Carenini, B.: Diurnal Variations of Systemic Venous Pressure, Am. J. Ophth. **39**:793, 1955.

24. Dobree, J. H.: Effect of Raised Ocular Tension on the Episcleral Vessels, Brit. J. Ophth. **38**:500, 1954.

25. von Sallmann, L., and Lowenstein, O.: Responses of Intraocular Pressure Blood Pressure, and Cutaneous Vessels to Electric Stimulation in the Diencephalon, Am. J. Ophth. **39**:11 (April, Pt. II) 1955.

26. Kaneda, S.: Effect of Retrobulbar Injections of Some Medicaments upon the Ocular Tension, Acta Soc. ophth. japon. **58**:1575, 1954.

27. Stepanik, J.: The Pathogenesis of Diurnal Variations in the Intraocular Pressure, Klin. Monatsbl. Augenh. **125**:737, 1954.

28. Lebedinskaia, E. I.: The Functional Condition of the Cortex in Glaucoma, Vestnik oftal. **32**:24, 1953.

29. Wiseman, R. D., and Moore, D. E.: Allergy as a Cause of Glaucoma, J. Allergy **25**:355, 1954.

30. Maslansky, E.: Diet Records of 62 Glaucoma Patients, Sight-Saving Rev. **25**:22, 1955.

31. Schmerl, E., and Steinberg, B.: Quantitative Effects of Miopiesin and Hyperpiesin on Intraocular Pressure, Am. J. Ophth. **39**:547, 1955.

32. Schmerl, E.; Dietz, A. A., and Steinberg, B.: Mechanism of Miopiesin Formation, Am. J. Ophth. **39**:684, 1955.

33. Ambrosio, A.: Testicular Function in Glaucoma, Gior. ital. oftal. **7**:517, 1954.

34. Urrets Zavalia, A.: Etiopathogenesis of Chronic Simple Glaucoma, Arch. opht. **13**:749, 1953.

35. Brand, I.: The Incidence of Vascular Disease in Glaucoma Patients, Ophthalmologica **128**:281, 1954.

36. Sokolowski, S.: Behavior of the Organ of Hearing and Balance in Patients with Glaucoma, Otolaryng. polska **7**:307, 1953.

37. ten Doesschate, J., and Lansberg, M. P.: Glaucoma and the Function of the Labyrinth, Bull. Soc. belge opht. **107**:205, 1954.

38. Desvignes, P., and Chardin, E.: Heredity in Primary Glaucoma, Arch. opht. **14**:587, 1954.

39. Penzani, B.: Heredity of Late Juvenile Glaucoma, Gior. ital. oftal. **84**:53, 1955.

40. Funder, W.: The Somatotype in Primary Glaucoma, Klin. Monatsbl. Augenh. **125**:262, 1954.

41. Huerkamp, B., and Zieglitz, W.: Ozone Content of the Air and Glaucoma, von Graefes Arch. Ophth. **154**:507, 1953.

42. Cristini, G.: The Oxygen Uptake of the Uvea in the Glaucomatous Eye, Ann. ocul. **187**:401, 1954.

43. Alajmo, B., and Simonelli, M.: Considerations in 3 Cases of Chiasmal Syndrome, Diagnosed and Treated as Chronic Simple Glaucoma, Gior. ital. oftal. **7**:281, 1954.

44. Bailbe, N.: Glaucomatous Excavation of von Graefe Connected with the Syndrome of Morgagni-Morel, Estud. inform. oftal. **4**:13, 1953.

45. Comberg, W.: Glaucoma Without Hypertension, Klin. Monatsbl. Augenh. **125**:257, 1954.

46. Foote, F. M.: Causes of Blindness in the United States of North America, Guildcraft **29**:20, 1955.

47. Björnsson, G.: Prevalence and Causes of Blindness in Iceland, Am. J. Ophth. **39**:202, 1955.

48. Wolpaw, B. J., and Sherman, A. W.: The Cleveland Glaucoma Survey, Sight-Saving Rev. **24**:139, 1954.

49. Alearts, M. L.: The Atrophies of the Temporal Iris-Quadrant in Chronic Glaucoma, Bull. Soc. belge opht. **107**:219, 1954.

50. Sengupta, M.: Neovascularization of the Disc in Chronic Simple Glaucoma, Brit. J. Ophth. **38**:685, 1954.

51. Schmidt, I.: Diagnostic Value of Foveal Entoptic Phenomena in Chronic Glaucoma, A. M. A. Arch. Ophth. **52**:583, 1954.

52. Zeller, R. W., and Christensen, L.: Routine Tonometry as Part of the Physical Examination, J. A. M. A. **154**:1343, 1954.

53. Gunderson, T.: Glaucoma and Amblyopia ex Anopsia, Two Preventable Forms of Blindness, J. A. M. A. **156**:933, 1954.

54. Weekers, R.; Prijot, E.; Delmarcelle, Y., and Gustin, J.: Physiologic and Pathologic Determinant Causes in the Control of Intraocular Hypertension in Chronic Simple Glaucoma, Bull. Soc. belge opht. **107**:208, 1954.

55. Suda, K.; Inamochi, J., and Ikuta, M. A.: A Study of the Essential Hypotony of the Eye, Acta Soc. ophth. japon. **58**:1231, 1954.

56. Rohrschneider, W., and Kuechle, H. J.: The Standard Error in Tonometry, Ophthalmologica **128**:369, 1954.

57. New Calibration Scale for Schiøtz, Gradle-Schiøtz, and McLean Tonometers, A. M. A. Arch. Ophth. **53**:160, 1955.

58. Jackson, C. R. S.: A New Calibration Scale for Schiøtz, Gradle-Schiøtz, and McLean Tonometers, Brit. J. Ophth. **39**:56, 1955.

59. Jackson, C. R. S.: Calibration of Tonometers, Brit. J. Ophth. **39**:368, 1955.

60. Posner, A.: The Basis of Tonometry, Eye, Ear, Nose & Throat Month. **34**:121, 1955.

61. Mamelock, A., and Posner, A.: Measurements of Corneal Elasticity, Am. J. Ophth. **39**:817, 1955.

62. Wiegersma, G.: Elastometry of the Eye, Am. J. Ophth. **39**:811, 1955.

63. Dreisler, K. K.: Sterilization of Tonometers, A. M. A. Arch. Ophth. **53**:860, 1955.

64. Rosner, R. S.: New Germicidal Tonometer Stand, A. M. A. Arch. Ophth. **53**:889, 1955.

65. Leydhecker, W.: Reliability of Provocative Tests in Glaucoma, Klin. Monatsbl. Augenh. **125**:539, 1954.

66. Leydhecker, W.: A Provocative Test for Glaucoma with Tolazoline (Priscoline), Klin. Monatsbl. Augenh. **125**:57, 1954.

67. Leydhecker, W.: Effect of Homatropine upon the Tension of the Normal and the Glaucomatous Eye, von Graefes Arch. Ophth. **155**:386, 1954.

68. Leydhecker, W.: Influence of Coffee upon Ocular Tension, Am. J. Ophth. **39**:700, 1955.

69. Leydhecker, W., and Niesel, P.: Statistical Evaluation of the Physiologic Limits of Provocative Tests for Glaucoma, Klin. Monatsbl. Augenh. **125**:458, 1954.

70. Campbell, D. A.; Gloster, J., and Tonks, E. L.: Some Observations of the Water Drinking Test in Glaucomatous and Non-Glaucomatous Subjects, Brit. J. Ophth. **39**:193, 1955.

71. Higgitt, A., and Smith, R.: Reading Test in Glaucoma, Brit. J. Ophth. **39**:103, 1955.

72. del Río Cabañas, J. L., and Cadeñas, U.: The Value of Kleinert's Compensation Maximum in the Diagnosis of Early Glaucoma, Arch. Soc. oftal. hispano-am. **14**:631, 1954.

73. Caselli, F.: The Findeisen Test in Glaucoma, Arch. ottal. **58**:67, 1954.

74. Pau, H.: A Rise in Blood Pressure as a Provocative Test for Glaucoma, Klin. Monatsbl. Augenh. **125**:45, 1954.

75. Grant, W. M., and Trotter, R. R.: Tonographic Measurements in Enucleated Eyes, A. M. A. Arch. Ophth. **53**:191, 1955.

76. Stepanik, J.: Diurnal Tonographic Variations and Their Relation to Visible Aqueous Outflow, Am. J. Ophth. **38**:629, 1954.

77. Andreani, D.: Baxter's Compression Test Compared with Provocative Tests of Bloomfield and Lambert, Schmidt, and Sugar in Normal and Glaucomatous Eyes, Ann. ottal. e clin. ocul. **80**:261, 1954.

78. Suda, K.; Inamochi, J., and Ikuta, M.: Local Regulation of Ocular Tension in 2 Types of Primary Glaucoma, One Controlled by Miotics, Another, So-Called Low-Tension Glaucoma, Acta Soc. ophth. japon. **58**:633, 1954.

79. François, J., and Verriest, G.: Field Defects in Glaucoma, Ann. ocul. **187**:985, 1954.

80. Suda, K.; Oyama, T., and Miyata, N.: Diagnostic Value of Red Visual Field in Early Glaucoma, Especially Under Low Illumination, Acta Soc. ophth. japon. **58**:642, 1954.

81. Miles, P. W., and Trapp, C. W.: Variations in Quality for Flicker Fusion Field Technique, Am. J. Ophth. **39**:171, 1955.

82. Irvine, A. R.: Disc Changes in Glaucoma, Tr. Pacific Coast Oto-Ophth. Soc. **34**:159, 1953.

83. Huerkamp, B., and Pohle, H.: The Intraocular Pressure During the Second Half of the Night, Klin. Monatsbl. Augenh. **124**:296, 1954.

84. Goldmann, H.: Two Lectures on Biomicroscopy of the Eye, Berne, Rösch, Vogt and Co., 1954.

85. Burian, H. M.; Braley, A. E., and Allen, L.: Visibility of the Ring of Schwalbe and the Trabecular Zone, A. M. A. Arch. Ophth. **53**:767, 1955.

86. Allen, L.; Burian, H. M., and Braley, A. E.: The Anterior Border Ring of Schwalbe and the Pectinate Ligament, A. M. A. Arch. Ophth. **53**:799, 1955.

87. Kravitz, D.: A Further Study of the Anterior Angle, Am. J. Ophth. **38**:622, 1954.

88. Grant, W. M., and Chandler, P. A.: An Arrangement for Gonioscopy During Surgery, A. M. A. Arch. Ophth. **52**:454, 1954.

89. Goodstein, S.; Cinotti, A.; Cholst, M., and Goeller, J.: A Technique for Goniophotography, A. M. A. Arch. Ophth. **53**:650, 1954.

90. Weinstein, P., and Forgács, J.: Clinical Aspects of Permeability of the Blood-Aqueous Barrier, Am. J. Ophth. **38**:377, 1954.

91. Askovitz, S. I.: Electrical Control Assembly for Slitlamp Biomicroscope, Am. J. Ophth. **39**: 571, 1955.

92. Thiel, R.: The Medical Therapy of Primary Glaucoma, Klin. Monatsbl. Augenh. **125**:513, 1954.

93. Knighton, W. S.: Management of Open-Angle Glaucoma, New York J. Med. **54**:3096, 1954.

94. McBain, E. H.: Diagnosis and Treatment of Glaucoma, California Med. **81**:231, 1954.

95. Sugar, H. S.: The Value of a Social Worker in a Glaucoma Clinic, Ophth. ibero-am. **16**:213, 1954.

96. Friedenwald, J. S.: Carbonic Anhydrase Inhibition and Aqueous Flow, Am. J. Ophth. **39**: 50 (April, Pt. II) 1955.

97. Becker, B.: The Mechanism of the Fall in Intraocular Pressure Induced by the Carbonic Anhydrase Inhibitor Diamox, Am. J. Ophth. **39**: 177 (Feb., Pt. II) 1955.

98. Vogelius, H., and Brun, C.: Glaucoma Treated with Diamox, Acta ophth. **32**:537, 1954.

99. Breinin, G. M., and Görtz, H.: Carbonic Anhydrase Inhibitor Acetazoleamide (Diamox), A. M. A. Arch. Ophth. **52**:333, 1954.

100. Green, H.; Capper, S.; Bocher, C., and Leopold, I. H.: Effect of Acetazoleamide on Carbonic Anhydrase Activity of the Anterior Uvea of the Rabbit Eye, A. M. A. Arch. Ophth. **52**:758, 1954.

101. Green, H.; Bocher, C.; Colman, A., and Leopold, I. H.: Carbonic Anhydrase and the Maintenance of Intraocular Tension, A. M. A. Arch. Ophth. **53**:463, 1955.

102. Green, H.; Bocher, C., and Leopold, I. H.: Carbonic Anhydrase and the Elaboration of Bicarbonate Ion in the Rabbit Eye, A. M. A. Arch. Ophth. **53**:472, 1955.

103. Green, H.; Bocher, C., and Leopold, I. H.: Determination of Acetazoleamide in the Aqueous Humor of Rabbits, A. M. A. Arch. Ophth. **53**:478, 1955.

104. Kinsey, V. E.; Camacho, E.; Cavanaugh, G. A.; Constant, M., and McGinty, D.: Dependence of IOP-Lowering Effect of Acetazoleamide on Salt, A. M. A. Arch. Ophth. **53**:680, 1955.

105. Weinstein, P.: Oral Therapy of Glaucoma, Acta med. **7**:223, 1955.

106. Kleinert, H.: The Influence of Acetazoleamide (Diamox) on the Increased Intraocular Pressure, Klin. Monatsbl. Augenh. **125**:271, 1954.

107. Foss, R. H.: Local Application of Diamox, Am. J. Ophth. **39**:336, 1955.

108. Demers, A., and Monfette, C.: Effect of Diamox on Ocular Tension, Canad. M. A. J. **72**: 529, 1955.

109. Murphy, E.: Diamox in Cataract Wound Healing, Am. J. Ophth. **39**:86, 1955.

110. Posner, A.: Atypical Response to Pilocarpine in a Case of Narrow Angle Glaucoma, Eye, Ear, Nose, & Throat Month. **34**:520, 1955.

111. Leydhecker, W.: Gonioscopic Studies During Increase in Ocular Tension Following the Use of Miotics and After Reading, von Graefes Arch. Ophth. **155**:255, 1954.

112. Bayo y Bayo, J., and de la Peña, A.: Action of Diisopropyl-*p*-Nitrophenyl Phosphate (Mintacol) in Glaucoma, Arch. Soc. oftal. hispano-am. **14**:415, 1954.

113. Cascio, G.: Biological Aspects of the Antiglaucomatous Activity of Furtrethonium-*p*-Toluenesulfonate (Fisostina), Rass. ital. ottal. **22**:577, 1953.

114. Junghanss, K.: Treatment of Glaucoma with Eustigmin, Deutsche Gesundhwes. **9**:629, 1954.

115. Westsmith, R. A., and Abernathy, R. E.: Detachment of the Retina with Use of Diisopropyl Fluorophate in Treatment of Glaucoma, A. M. A. Arch. Ophth. **52**:779, 1954.

116. Zicha, J., II: Glaucoma-Iritis? Československ. oftal. **9**:315, 1953.

117. Andreani, D.: Secondary Rise of the Intraocular Tension Produced by Isofluorophate (D. F. P.) in Glaucomatous Subjects: Observations with Regard to the Conditions of the Iridocorneal Angle, Ann. ottal. e clin. ocul. **80**:341, 1954.

118. Primrose, J.: Dibenzyline in Glaucoma, Brit. J. Ophth. **39**:307, 1955.

119. Weekers, R.; Prijot, E., and Gustin, J.: Measurement of the Resistance to Aqueous Outflow: VI. Mode of Action of Adrenaline in Chronic Glaucoma, Ophthalmologica **128**:213, 1954.

120. Weekers, R.; Prijot, E., and Gustin, J.: Recent Advances and Future Prospects in the Medical Treatment of Ocular Hypertension, Brit. J. Ophth. **38**:742, 1954.

121. François, J.: Cortisone and Ocular Tension, Ann. ocul. **187**:805, 1954.

122. François, J.: Cortisone and Ocular Tension, Bull. Soc. belge opth. **106**:190, 1954.

123. Laval, J., and Collier, R., Jr.: Elevation of Intraocular Pressure Due to Hormonal Steroid Therapy in Uveitis, Am. J. Ophth. **39**:175, 1955.

124. Colombi, C.: Cortisone and Ocular Tonus, Rass. ital. ottal. **23**:63, 1954.

125. Sébas, S. R.: Progesterone in Glaucoma, Rev. brasil. oftal. **13**:83, 1954.

126. McGuire, W. P.: A Further Report on the Effect of Dicumarol on the Visual Fields in Glaucoma, Tr. Am. Ophth. Soc. **51**:67, 1953.

127. Bettini, L., and Gallia, L.: Hypotony After Retrobulbar Novocaine and Epinephrine Injection, Boll. ocul. **33**:771, 1954.

128. de Roetth, A., Jr., and Carroll, F. D.: Effect of Retrobulbar Procaine Injection on Aqueous Humor Dynamics, A. M. A. Arch. Ophth. **53**:399, 1955.

129. Sanna, M.: Effect of Nicotine on Intraocular Pressure and on the Angioscotoma of the Glaucomatous Eye, Boll. ocul. **33**:31, 1954.

130. Bietti, G. B.: The Diagnostic Problem of Glaucoma, Irish J. M. Sc. **342**:237, 1954.

131. Schumacher, H.: The Fall of the Intraocular Pressure After Salicylic Acid, Klin. Monatsbl. Augenh. **125**:299, 1954.

132. Sakamoto, Y.: The Effect of Prophylactics for Motion Sickness on the Intraocular Pressure, Acta Soc. ophth. japon. **58**:1218, 1954.

133. Sédan, J.: Results of 262 Antiglaucoma Fistulizing Operations Followed Up for 4 to 32 Years After Operation, Ann. ocul. **187**:409, 1954.

134. Sédan, J.: Individual and Familial Factors in the Slow Obliteration of Antiglaucomatous Fistulas, Ann. ocul. **187**:31, 1954.

135. LeGrand, J.: Cataracts and Antiglaucomatous Operations, Ann. ocul. **187**:25, 1954.

136. Williamson-Noble, F. A.: Cataract Extraction After a Glaucoma Operation, Tr. Ophth. Soc. U. Kingdom **73**:585, 1953.

137. Hallermann, W.: An Indication for Surgery in Primary Glaucoma, Klin. Monatsbl. Augenh. **124**:513, 1954.

138. Trotter, R. R.: Peripheral Iridectomy in Angle Closure Glaucoma, Am. J. Ophth. **39**:409, 1955.

139. Posner, A.: Indications for Surgery in Narrow Angle Glaucoma, Eye, Ear, Nose & Throat Month. **34**:193, 1955.

140. Posner, A.: Treatment of Narrow Angle Glaucoma, Eye, Ear, Nose & Throat Month. **34**:393, 1955.

141. Posner, A.: Treatment of Narrow Angle Glaucoma, Eye, Ear, Nose & Throat Month. **34**:454, 1955.

142. Stoentchev, S. P.: Iridectomy ab Externo, Chirurgia, Sofia **5**:362, 1952.

143. Wudka, E., and Leopold, I. H.: Studies on Experimental Glaucoma, A. M. A. Arch. Ophth. **53**:487, 1955.

144. Sbordone, G.: The Effect of Iridectomy on the Permeability of the Blood-Aqueous Barrier, Rass. ital. ottal. **23**:451, 1954.

145. Mackie, E. G., and Rubinstein, K.: Iridencleisis in Congestive Glaucoma, Brit. J. Ophth. **38**:641, 1954.

146. Gildemyn, M. H.: Iridencleisis in Secondary Glaucoma Following Cataract Extraction, Bull. Soc. belge opht. **107**:268, 1954.

147. Guenther, G., and van Beuningen, E. G. A.: Regulation of the Ocular Tension Following Iridencleisis, von Graefes Arch. Ophth. **155**:1, 1954.

148. Stanković, M., and Stanković, I.: Can One Avoid Certain Complications in Fistulizing Operations for Primary Glaucoma? Ann. ocul. **187**:726, 1954.

149. Stanković, M.: Subconjunctival Injections of Sterile Air in Operations with Fistulization, Ann. ocul. **186**:857, 1953.

150. Posner, A.: Technique of Peripheral Iridencleisis, Eye, Ear, Nose & Throat Month. **34**:55, 1955.

151. Wenaas, E. J., and Stertzbach, C. W.: Cataract Extraction with Iris Inclusion, Am. J. Ophth. **39**:71, 1955.

152. Cristini, G., and Pentini, G.: Is Iridencleisis a Revascularization of the Anterior Uvea? Rass. ital. ottal. **23**:272, 1954.

153. Caselli, F.: Experimental Researches on the Immediate and Late Results of Iridencleisis, Gior. ital. oftal. **7**:440, 1954.

154. Caselli, F.: Experimental Investigations on the Permeability of the Blood-Aqueous Barrier in Eyes Having Undergone Various Antiglaucomatous Operations, Arch. ottal. **58**:279, 1954.

155. Klemens, F.: The "Test Operation" in Chronic Glaucoma, Klin. Monatsbl. Augenh. **125**:531, 1954.

156. Kalt, M.; Decaudin, A., and Loisillier, F.: Torpid Iritis Following Antiglaucomatous Operations, Bull. Soc. opht. France **2**:193, 1954.

157. Roig, A.: Use of a Surgical Appliance in Elliot's Operation, Arch. Soc. oftal. hispano-Am. **14**:797, 1954.

158. Stallard, H. B.: Late Restoration of Anterior Chamber by Surgery, Brit. J. Ophth. **39**:112, 1955.

159. Dusseldorf, M., and Piantoni, G.: Repeated Trephine Operation for Glaucoma, Arch. oftal. Buenos Aires **29**:437, 1954.

160. Foroni, M.: Triangular Valve (or Inverted T) Sclerotomy in Glaucoma, Ann. ocul. **187**:369, 1954.

161. Kleinert, H.: The Aqueous Outflow After Cyclodialysis, Ophthalmologia **128**:44, 1954.

162. Kamel, S.: The Surgical Control of Glaucoma Secondary to Essential Atrophy of the Iris, Bull. Ophth. Soc. Egypt **46**:243, 1953.

163. Nano, H. M.; Frigerio, E., and Scenna, M.: Submuscular Sclerectocyclodialysis in Glaucoma, Arch. oftal. Buenos Aires **29**:497, 1954.

164. Maeder, G.: Perforating Retrociliary Diathermy, Ophthalmologica **127**:368, 1954.

165. Bartolome, A.: Nonperforating Retrociliary Diathermy in the Treatment of Hypertensive Uveitis, Arch. Soc. oftal. hispano-Am. **13**:1315, 1953.

166. Sokolić, P.: Further Experience with the Combined Cyclodiathermy Nonperforativa cum Cyclodialysis Circumscripta in Various Types of Glaucoma, Klin. Monatsbl. Augenh. **123**:30, 1953.

167. Weekers, L.: Nonperforating Retrociliary Diathermy in the Treatment of Ocular Hypertension, Ann. ocul. **187**:318, 1954.

168. Cascio, G.: The Value of Cyclodiathermy in Infantile Glaucoma, Rass. ital. ottal. **23**:445, 1954.

169. Covell, L. L., and Batungbacal, R. T.: Cyclodiathermy in Glaucoma, Am. J. Ophth. **40**:77, 1955.

170. Szymanski, J.: Electrolytic Cyclocoagulation, Arch. brasil. oftal. **14**:131, 1951.

171. Funder, W.: Operative Treatment of Hydrophthalmos, Klin. Monatsbl. Augenh. **124**:516, 1954.

172. Cusick, P. L.: A Goniotomy Knife, Tr. Am. Acad. Ophth. **58**:594, 1954.

173. Cusick, P. L.: Cyclodialysis with Goniotomy in Congenital Glaucoma, Am. J. Ophth. **38**:712, 1954.

174. Kleinert, H.: The Posterior Sclerectomy, Klin. Monatsbl. Augenh. **126**:31, 1955.

175. Barkan, O.: Pathogenesis of Congenital Glaucoma, Am. J. Ophth. **40**:1, 1955.

176. Siliato, F.: Gonioscopy in Some Congenital Anomalies of the Eyeball, Ann. ottal. e clin. ocul. **80**:349, 1954.

177. Allen, L.; Burian, H., and Braley, A.: A New Concept of the Development of the Anterior Chamber Angle, A. M. A. Arch. Ophth. **53**:783, 1955.

178. Meyer, S.; Shaffer, R. N.; Scheie, H. G.; Barkan, O., and Haas, J. S.: Symposium on Congenital Glaucoma, Tr. Am. Acad. Ophth. **59**:309, 1955.

179. Robertson, E. N., Jr.: Therapy of Congenital Glaucoma, A. M. A. Arch. Ophth. **54**:55, 1955.

180. Tyner, G. S.: Report on 13 Eyes Treated by Goniopuncture, A. M. A. Arch. Ophth. **54**:59, 1955.

181. Cramer, F. E. K.: Present-Day Treatment of Congenital Glaucoma, Opht. ibero-am. **16**:208, 1954.

182. Brockhurst, R. J.: The Intraocular Pressure of Premature Infants, Am. J. Ophth. **39**:808, 1955.

183. Kronfeld, P. C.: A Tonographic Study of the Glaucoma Due to Delayed Restoration of the Anterior Chamber After Cataract Extraction, Am. J. Ophth. **39**:147 (April, Pt. II) 1955.

184. Flocks, M.; Littwin, C. S., and Zimmerman, E. Z.: Phacolytic Glaucoma, A. M. A. Arch. Ophth. **54**:37, 1955.

185. Wilson, R. P.: Capsular Exfoliation and Glaucoma Capsulare, Tr. Ophth. Soc. New Zealand, Supp. 8, 1953.

186. Ingman, W.: Concussion Glaucoma, Brit. J. Ophth. **38**:747, 1954.

187. Chinaglia, V.: Variations of the Tension in Eye Injuries and Simple Traumatic Glaucoma, Ann. ottal. e clin. ocul. **81**:79, 1955.

188. Cohen, M. H., and Chamlin, M.: Uveitis with Glaucoma and Retrobulbar Neuritis, Am. J. Ophth. **38**:615, 1954.

189. Mattson, R.: Glaucomatocyclitic Crises, Acta ophth. **32**:523, 1954.

190. Zewi, M.: The Syndrome of Glaucomatocyclitic Crises, Ann. chir. et gynaec. Fenniae **43**: 539, 1954.

191. de Ferrari, G.: A Case of Essential Iris Atrophy Associated with Glaucoma Treated Surgically with Good Result, Boll. ocul. **33**:290, 1954.

192. Sivasubramaniam, P., and Hoole, T.: Bilateral Essential Atrophy of the Iris, Brit. J. Ophth. **39**:119, 1955.

193. Marchi, F.: Rapid Changes in the Depth of Congenital Glaucoma. Opht. ibero-am. 16ã208, with Subluxated Lens, Boll. ocul. **33**:842, 1954.

194. Wollin, N. C.; Yourish, N., and Nathaniel, A.: Bilateral Ectopia Lentis in a Dwarf, Am. J. Ophth. **39**:569, 1955.

# News and Comment

## GENERAL NEWS

**Stanford Spring Postgraduate Conference.**—Stanford University School of Medicine will present the annual Postgraduate Conference in Ophthalmology from March 19 through March 23, 1956. Registration will be open to physicians who limit their practice to the treatment of diseases of the eye, or the eye, ear, nose, and throat. In order to allow free discussion by members of the Conference, registration will be limited to 30 physicians.

Instructors will be Dr. David L. Bassett, Dr. D. K. Pischel, Dr. Jerome W. Bettman, Dr. Max Fine, Dr. Earle H. McBain, and Dr. Arthur J. Jampolsky.

Programs and further information may be obtained from the office of the Dean, Stanford University School of Medicine, 2398 Sacramento St., San Francisco 15.

# News and Comment

## GENERAL NEWS

**The Research Study Club of Los Angeles.**—The Research Study Club of Los Angeles announces its 25th Annual Mid-Winter Clinical Convention in Ophthalmology and Otolaryngology, Jan. 16 through Jan. 27, 1956.

For the ear-nose-throat program, the main guest lecturers will include Dr. Benjamin H. Shuster, Professor of Otolaryngology, Graduate School of Medicine, University of Pennsylvania, Philadelphia; Dr. French K. Hansel, Director, Hansel Foundation, and Associate Professor of Otolaryngology, Washington University, St. Louis; Dr. Edmund P. Fowler Jr., Professor of Otolaryngology, Columbia University College of Physicians and Surgeons, and Director of Otolaryngological Service, Presbyterian Hospital, New York, and Chauncey D. Leake, Ph.D., Professor of Pharmacology and Assistant Dean, Ohio State University Health Center, Columbus, Ohio.

The main guest lecturers for the eye program will be Dr. F. Bruce Fralick, Professor of Ophthalmology and Head of the Department, University of Michigan, Ann Arbor; Dr. Harold F. Falls, Associate Professor of Ophthalmology, and Associate Geneticist, Institute of Human Biology, University of Michigan, Ann Arbor, and Dr. David O. Harrington, Associate Clinical Professor of Ophthalmology, University of California, Berkeley.

Instruction courses in ophthalmology will be presented by Dr. Harrington on flicker-fusion perimetry; Dr. Homer E. Smith, of Salt Lake City, on anterior chamber hemorrhages; Dr. James N. Greear Jr., of Reno, on intraocular tumors; Dr. Max Fine, of San Francisco, on keratoplasty, and Dr. W. C. Cameron, of Tacoma, on cataract surgery.

The first week will be devoted to the ear, nose, and throat — from Monday to Friday, Jan. 16 through Jan. 20. The eye week will cover Monday to Friday, Jan. 23 through Jan. 27. Those of us who confine our work to only one of these specialties may complete either subject in one week, or remain for the full two weeks.

Motion pictures of ear-nose-throat subjects will be shown on Monday, Tuesday, Thursday, and Friday, Jan. 16, 17, 19, and 20, 3:00 to 4:00 p. m. Eye subjects will be presented on Wednesday afternoon of the eye week.

On Thursday evening, Jan. 19, at 7 p. m., the annual banquet of the Los Angeles Society of Ophthalmology and Otolaryngology will honor the guest lecturers of that week, in the El Venado Room of the Elks Club.

The American Laryngological, Rhinological, and Otological Society, Western Section, will hold its annual meeting in San Francisco between the two weeks of this Convention, on Saturday, Jan. 21, 1956. This will permit our members to attend the San Francisco meeting and return to Los Angeles for the eye week. Programs of the San Francisco meeting will be available at the registration desk at the Elks Club.

It is advised that you write for reservations at an early date to Mr. R. B. Philbin, Manager of the Elks Club, 607 S. Parkview St., Los Angeles 57.

Each applicant must be a member, in good standing, of the American Medical Association in order to become eligible for attendance at the Convention. The fee for the entire two weeks, or any part of it, is $100 and includes the cost of all luncheons. Checks should be made payable to "Mid-Winter Clinical Convention" and mailed to Norman Jesberg, M.D., treasurer, 500 S. Lucas Ave., Los Angeles 17.

**New Review Journal in Ophthalmology.**—A new review journal, *The Survey of Ophthalmology*, will begin publication in February, 1956. Frank W. Newell, Professor of Ophthalmology at the University of Chicago, is editor, and Williams & Wilkins Company, of Baltimore, are the publishers. The journal will sift, condense, and comment on the world ophthalmic literature and will present review

articles. Advisory editors are William L. Benedict, William B. Clark, F. Herbert Haessler, Peter C. Kronfeld, Algernon B. Reese, Phillips Thygeson, and Derrick Vail. Contributing editors are Henry F. Allen, Bernard Becker, Alson E. Braley, Hermann M. Burian, Harold F. Falls, George M. Haik, John W. Henderson, John Woodworth Henderson, Bertha Klien, James E. Lebensohn, Albert N. Lemoine Jr., Irving H. Leopold, Otto Lowenstein, P. Robb McDonald, Austin Riesen, Theodore E. Sanders, David Schoch, Daniel Snydacker, H. Saul Sugar, Edwin F. Tait, Gordon L. Walls, and Arthur Linksz.

*The Survey of Ophthalmology* will appear bimonthly, in the months of February, April, June, August, October, and December. The subscription is $9.00 annually.

**Fifth Congress of Pan-American Medical Women's Alliance.**—The Fifth Congress of the Pan-American Medical Women's Alliance will be held in Santiago and Viña del Mar, Chile, March 6-14, 1956. Opportunities for sightseeing and visits to medical programs in Mexico, Salvador, Panama, Chile, Bolivia, and Peru have been arranged.

Information may be obtained from the secretary, Dr. Eva Dodge, 2124 W. 11th St., Little Rock, Ark., or from the program chairman, Dr. Eva Cutright, Wooster, Ohio.

**Friedenwald Memorial Fund.**—In recognition of the profound interest in research and the brilliant accomplishments of Dr. Jonas S. Friedenwald, the trustees of the Association for Research in Ophthalmology announce the establishment of the "Friedenwald Memorial Fund." The fund will be used for awards for meritorious research in ophthalmology and related sciences.

Contributions to the fund may be sent to David G. Cogan, M.D., chairman of the Committee, 243 Charles St., Boston, or to Bernard Becker, M.D., 640 S. Kingshighway Blvd., St. Louis 10, or to Dr. V. Everett Kinsey, Kresge Eye Institute, 690 Mullett St., Detroit.

# Books

**The Neuroanatomical Basis for Clinical Neurology.** By Talmadge L. Peele, M.D. Price, $12.50. Pp. 564, with 313 illustrations. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 18, 1954.

The basis of neurological diagnosis is neuroanatomy, and an anatomist with a physiological point of view and some clinical training is in a favored position to produce the ideal textbook of neurology. This book seems to be the product of that happy combination of circumstances, and, judged by the chapters which deal with neuro-ophthalmology, the author has well achieved his purpose of combining descriptive neuroanatomy, neurophysiology, and clinical neurology.

The parts of the book which will be most useful to ophthalmologists are the sections on the prefrontal regions of the frontal lobes, the chapter on the cranial nerves, and the chapter on the visual pathways and the occipital lobe. Much new material is included, and the printing and illustrations are excellent.

**Advances in Ophthalmology.** By Streif. Price, 39.50 Swiss francs. Pp. 323, with 42 illustrations. S. Karger, AG., Arnold Böcklinstrasse 25, Basel, Switzerland, 1954.

The fourth edition of this continued report on the advances made in ophthalmology covers the following subjects:

Orbital Implants, D. P. Choyce, London

Gonioscopy, J. François, Gent

Physical Optics and Dioptrics, M. C. Colenbrander, Leiden

Teratology of the Eye Itself and Its Relation to the Rest of the Organism, P. J. Waardenburg, Leiden

Embryology of the Eye in Relation to General Somatic Embryology, P. J. Waardenburg, Leiden

Cornea and Sclera: Review of the Literature from 1946 to 1951, Pt. I, S. Forni, Geneva

Only two sections are in English, the one on Orbital Implants and the one on Physical Optics, so that the usefulness of this book is limited to those who read both German and French, as well as English. Undoubtedly the European ophthalmologists will find this of greater value than we in this country, who are not so facile in languages. As usual, the printing and illustrations are excellent, and the book serves a useful purpose in bringing isolated subjects up-to-date.

**Potencialización farmacodinamica en oftalmologia.** By Joaquin Barraquer Moner. Pp. 293. Publicaçiones Monograficas del Instituto Barraquer, Barcelona, Spain, 1955.

Taking as a basis the theories of Laborit and Huguenard who in 1955 published the first results of a technique of anesthesia, which they called "General Anesthesia Without General Anesthetic Agents," the author applies these results to anesthesia in ophthalmic surgery. This technique is based on the following three points: conscious suppression of pain; akinesia or suppression of the motor impulses to the striate muscles, and elimination of defense reflexes of the neurovegetative system. This is achieved with the following combination of pharmacological agents: barbiturates (phenobarbital [Luminal], pentobarbital [Nembutal] and thiopental [Pentothal]); ganglioplegics (diethazine [Diparcol], promethazine [Phenergan], hexamethonium, procaine, and chlorpromazine [Largactil]; analgesics (meperidine [Dolantin]); curare-like drugs (curare [Curarine]); parasympathicolytic agents (atropine); sympathicolytic agents (ergotamine and hydergine [three hydrogenated ergot alkaloids]), and local instillation anesthetics (tetracaine 2% and cocaine 10% solution). This book includes statistics of the cases in which this method was used, illustrations of ocular nerve supply, and photographs of twenty cases showing the preoperative appearance and postoperative results.

**Understanding Surgery.** Robert E. Rothenberg, F.A.C.S., Editor. Price, $0.50. Pp. 620, including index, with 102 illustrations. Pocket Books, Inc., 630 Fifth Ave., New York 20, 1955.

The intent of this book is to allay the unnecessary fears and anxieties of patients about to undergo surgery. The author believes that many of these fears can be minimized by a frank and simple explanation of the things that the patient will experience during his stay in the hospital. It is undoubtedly true that ignorance creates fears and that physicians do not realize what a traumatic experience it is for most people to come to the hospital as a patient for the first time.

The author has had the assistance of seven co-authors in covering the entire field of surgery. The section on eye surgery has been done by Dr. Bernard L. Small, an Associate Attending Ophthalmologist at the Jewish Hospital in Brooklyn.

The purpose of the book is admirably carried out and, if it can be gotten to the right people at the right time, will undoubtedly be helpful. It would seem to the reviewer that the only possible way it could serve its purpose would be for hospitals to provide the book for each patient on admission. It would certainly be more helpful than the practice of one hospital the reviewer knows of, where a large volume embracing the history of the hospital is offered for light reading.

Each field is fairly well covered by presenting the main facts which the patient should know, followed by a series of questions and answers. The section on the eye covers surgery of the cornea and eyelids, cataract, strabismus, glaucoma, and retinal detachment, and the removal of an eye. While there are naturally many points which could be disagreed with by other surgeons. Each author has endeavored to omit all controversial questions and to give what would be average answers to the questions posed.

**Ageing—General Aspects.** Volume I. By G. E. W. Wolstenholme and Margaret Cameron, Editors for the Ciba Foundation. Price, $6.75. Pp. 255, including index, with 38 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1955.

This latest publication of the Ciba Foundation is the result of a colloquium on aging, its general aspects, by a well-known group of gerontologists, pathologists, and biologists. The Ciba Foundation is an educational and scientific charity founded in 1947 by the chemical and pharmaceutical firm of Ciba, with headquarters in Basel, Switzerland. As expressed by W. B. Bean, one of the members of the panel, a colloquium means "talking to each other." The value of all of the Ciba publications lies not only in the preeminence of the men who are invited to form a panel in their chosen field, but in the fact that they have an opportunity of "talking to each other," and this conversation is taken down verbatim, so that the reader may see for himself how the experts disagree with each other and in what ways they resolve these disagreements—sometimes, it is true, in agreeing to disagree.

This volume on aging is interesting reading, and of value to any physician who deals with elderly people, and this certainly includes the ophthalmologist. It does not deal specifically with any of the problems of our cataract patients, or how to treat the elderly, but poses the more academic questions of what constitutes aging and what constitutes senescence. The mental aspects of aging, the psychology of the aged, the effects of aging on respiratory function, and the incidence of certain vascular lesions of the skin with aging come as close as any of the separate presentations by the different authors to the problems of aging encountered by the practicing physician and surgeon, but all of the presentations contain valuable background information, and should be enjoyed by those who wish to keep their knowledge of general biology and medicine up-to-date.

# IT'S ONLY A TEMPLE

GUILD Rx OPTICIANS

A simple piece of metal or of zylonite but it can make the difference between a satisfied patient and a much needed correction discarded because of improper or careless fitting. In the hands of your GUILD OPTICIAN this temple becomes an integral part of the eye wear which you have prescribed for better vision.

# *Do you dispense glasses?*

We are one of the oldest, and most reputable wholesale opticians in the east, serving the discriminate ophthalmologist.

An inquiry from you will bring a representative at your convenience to outline our superior service plan.

## MAX ZADEK, INC.

*established 1904*

115 Fulton Street New York 38, N. Y.

YOUR
GUIDE TO
CURRENT PUBLICATIONS

Quarterly
Cumulative
Index Medicus

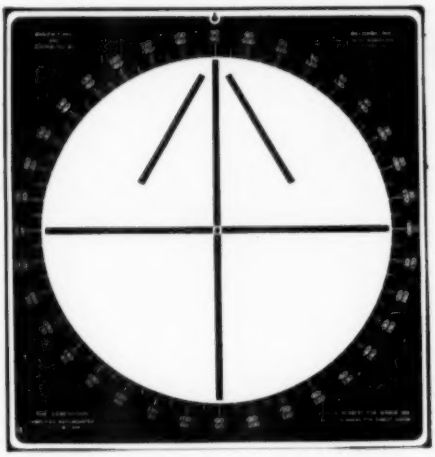
Divided into sections, one devoted to books and the other to periodical literature, the QUARTERLY CUMULATIVE INDEX MEDICUS contains a list of current publications alphabetized as to authors and subjects. The exact bibliographic reference is given under the author with titles in the original language, while titles under subjects are all in English. The index also includes a listing of journals, addresses and publishers.

The QUARTERLY CUMULATIVE INDEX MEDICUS appears twice a year; volumes are cloth bound and cover periodicals for six months as indicated on the publication. These two volumes will be a convenient and inclusive reference for current medical literature. Invaluable for practitioners, specialists, teachers, editors, writers, investigators, students and libraries.

WITH AUTHORS
AND SUBJECTS . . .

SUBSCRIPTION PRICE $20.00 PER YEAR
CANADIAN AND FOREIGN $22.00 PER YEAR

AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN • CHICAGO 10



(Actual size 13½" x 14")

# SIMPLIFIED ASTIGMOMETER

*(Lebensohn)*

**PLASTIC**

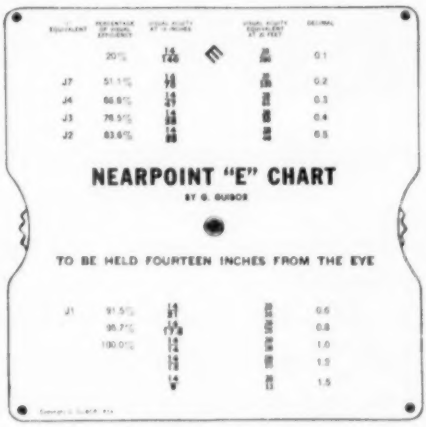
**WASHABLE**

**"NO COMPUTATION REQUIRED"**

CAN BE USED AT 10 OR 20 FEET

***Send for Literature***

**EACH $9.75**




Actual size 6" x 6"

## *New Near Chart*

GUIBOR Symbol Near Chart now available in durable and soilproof plastic. Gives distance equivalents, as well as quantitative measurements for near vision. E Symbol understood by all.

Place your order now.

**$3.25**

DISPENSING SERVICE

**Loop Office:**
111 N. Wabash, at Washington
9th Floor STate 2-5362
CHICAGO, ILL.

Austin Belgard INC.
(Formerly Belgard, Inc.)

*OPHTHALMIC OPTICIANS*
WHOLESALE & SERVICE

**Wilmette Office:**
1139 Central Avenue
WILMETTE, ILL.

***Now you can detect***

**intra-cranial lesions**

**affecting the optic tract . . . .**

***or rule them out—***

**in 3 or 4 minutes—**

**with the O'Brien Central Field Screening Tests**

"The Visual Tracts are subject to frequent involvement, secondary in nature, which often gives accurate clue to the pathology."—Importance of optic tract as indicator of possible pathology has been stressed by Krimsky, Traquair, Fuchs, Duke-Elder, etc.

*Tests for*

**Central Scotoma**

**Hemianopsia:** Homonymous, Binasal or Bitemporal

**Altitudinal Defects**

**Quadrant or Sector Defects**

When you're busy, you'll especially appreciate Dr. Miles O'Brien's screening tests . . . positive findings indicate the need for further investigation.

*Mail the coupon for circular.*

**KEYSTONE VIEW CO., Meadville, Pa.**

Please send Circular showing Charts of James Miles O'Brien, M.D., and giving his discussion of the diagnostic scope of Central Field Screening.

(Name) .....

(Address) .....



## The Berman Metal Locator

**An electromagnetic detecting device that quickly and accurately locates metallic foreign bodies, including magnetic intraocular foreign bodies. Metallic fragments are readily detected from a satisfactory distance through intervening bone, tissue and fluids. Probing or physical contact with the foreign body is not required for detection.**

**The thin sterilizable probe provides preoperative localization, "pin-point" accuracy within the incision and postoperative check.**

**Lends precision to foreign body surgery and greatly reduces surgical trauma.**

**BERMAN LABORATORIES**

**112-03 Rockaway Blvd. Ozone Park 20, N. Y.**


### NEW ORLEANS ACADEMY OF OPHTHALMOLOGY

The Sixth Annual Meeting of the New Orleans Academy of Ophthalmology will be held in New Orleans in the Roosevelt Hotel, January 3-6, 1956, featuring "Diseases and Surgery of the Lens." The registration fee of $75 includes associate membership in the Academy for the year 1956, as well as all other features of the convention. Hotel Reservations should be made EARLY by writing directly to the Roosevelt Hotel or to 211 S. Saratoga St., New Orleans, La.

*This baby sitter loses up to 63% of Vital Vision**

**Will she be caring for your kids . . . when it happens?**

*It won't be her fault—but she's bound to make a mistake. It could be deadly. Even with bifocals, she has lost 20/20 vision at intermediate—this vision may be vital. *We know how much she's lost.* You can have this information without cost. Our comprehensive study of visual loss in presbyopia is completed, and results are available. We respectfully suggest that you employ this chart of average losses in Vital Vision for bifocal wearers—carefully computed for you by age, by strength of Rx.

Never has there been such strong evidence for the consideration of CV lenses for bifocal patients 50 and over.

UNIVIS

write:

The UNIVIS LENS COMPANY
*Professional Service Department*
DAYTON, OHIO

Gonioscope

**Instrumentation for**

## MICRO-GONIOSCOPY and GONIOTOMY

**after Otto Barkan, M.D.**

| | |
|---|---|
| GONIOSCOPE (illustrated) floor model, for office and hospital surgery | $185.00 |
| CORNEAL MICROSCOPE B & L | 180.00 |
| CORNEAL MICROSCOPE Haag-Streit | 225.00 |
| Your own Corneal Microscope adapted to gonioscope | 10.00 |
| Otto Barkan Focal Illuminator (hand lamp) with plug in transformer | 42.50 |
| Otto Barkan-Koeppe Diagnostic Lens (for viewing the angle) small (infant) 16 & 17 mm (medium) 18 & 19 large (adult) 20 mm in glass | 45.00 |
| Otto Barkan Surgical Goniotomy Lens small (infant) med. (child and adult) | 45.00 |
| Otto Barkan Surgical Knife (latest model) | 9.75 |
| Otto Barkan Operating Lamp | 65.00 |
| Floor stand for above | 20.00 |

**PARSONS OPTICAL LABORATORIES, INC.**

**518–20 Powell Street** **San Francisco 2, Calif.**

**A necessity in every eye operating room and wherever eye injuries are treated.**

OPHTHALMOS

**Sterile, fully potent eye medications in the new**

**steridroppa**

trademark
pat. pend.

**Single Dose Disposable Dropper Unit**

**all important solutions required for ocular surgery** *available in the*

**write now for details to OPHTHALMOS, INC.**
**UNION CITY, N. J.**

# 5cc DROP-TAINER

## Isopto®-Cortisone

.5% AND 2.5%

## Isopto®-Hydrocortisone

.5% AND 2.5%

Sterile, buffered ophthalmic suspensions of Cortisone Acetate and Hydrocortisone Acetate for topical use. In *Methyl Cellulose* for more uniform suspension, more prolonged contact (5 to 6 times longer), and better dispersion when applied to the eye.

### ADVANTAGES OF DROP-TAINER PRODUCTS

- Sterile
- Stable
- Preserved against contamination
- Convenient to carry and use: better drop control
- Economical: non-spillable and non-breakable
- Uniform

Available from pharmacies and wholesale drug suppliers throughout the U.S.A. and Canada (Canadian Distributors, Imperial Optical Company, Toronto, Canada). Write for catalog descriptive of miotics, mydriatics, anesthetics, etc., supplied in Drop-Tainer.

**Alcon**

**LABORATORIES, INCORPORATED**
**FORT WORTH, TEXAS**

E. B. Meyrowitz

**SURGICAL INSTRUMENTS CO., INC.,**
**520 FIFTH AVENUE, NEW YORK 36, N. Y.**

LONDON — *ESTABLISHED 1875* — PARIS

## McLEAN TONOMETER

This is a most accurate instrument for measuring intraocular pressure. It is simple in construction and operation, has a direct reading scale. The scale shows normal and abnormal limits of tension in red and black.

***Supplied in case, $55.00***

### HERTEL EXOPHTHALMOMETER

Improved over the original German model, in that it has front surface mirrors which do away with parallax, this exophthalmometer enables the examiner to measure the degree of exophthalmos accurately and rapidly without assistance.

The right member slides over a calibrated millimeter rule. Each member has two mirrors mounted at right angles, one above the other. When the instrument is in position, with the two outer points in contact with the temporal margin of each orbit, the profile of the cornea is seen in one mirror and the scale in the other. The scale reading directly above the corneal images gives its protrusion in millimeters.

The separation of the two members is shown on the slide. All measurements of the same case must be made with the members separated to the same reading on the sliding scale.

Supplied in case.

**Price $55.00**

**If You Wear Glasses and Drive at Night**

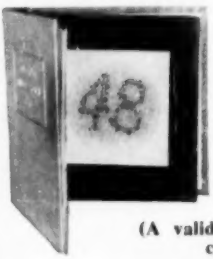
Notice how reflections from electric signs, street lights and headlights on the surfaces of your glasses are very annoying? These are "ghost images" that hamper clear vision and add to the chore of night driving.

MAY-O-LITE, a hard, durable, thin film of Magnesium Fluoride, helps make night driving easier.

*Complete Your Professional Service By Adding*

***The Best in Sight***
**MAY-O-LITE**
**Low Reflection Coating**

**MAY RESEARCH, INC., Box 1181, Minneapolis 1, Minn.**




**DVORINE**

**PSEUDO-**

**ISOCHROMATIC**

**PLATES**

**(A valid and reliable test for color blindness.)**

**Exclusive Features**

- **A test for color nomenclature, to distinguish the color blind from the color ignorant.**
- **A special section for testing very young children and illiterates.**
- **The set contains 23 plates with eight different color combinations, for the identification of specific confusion colors.**
- **The pages are mounted in a loose-leaf, six-ring cloth-covered binder, to permit the examiner to change the sequence of the plates to outwit the malingerer.**

Price of the set
**$12.00**
(with directions)
Less 5%, if check accompanies order.

**SCIENTIFIC PUBLISHING CO.**
**Dept. A, 2328 Eutaw Place, Baltimore 17, Md.**

# . . . the Joy of Giving

Christmas morning . . . and the rewards of giving are seeing the enraptured faces of children . . . and hearing their cries of joy.

The tinseled tree trembles with their bedlam, but to the ones who gave comes a calm that's the spirit of Christmas itself . . . the peace of the joy of giving.

**Titmus**

TITMUS OPTICAL CO., INC., PETERSBURG, VIRGINIA

# THE NEW MUELLER
*Electric*
# CORNEAL TREPHINE

**ORDER YOURS NOW**
**AT NEW SPECIAL LOW PRICE**

*Balanced—Smooth, Clean Cutting*
*Complete with Special Battery Box*

THE TREPHINE—A new model with a specially designed little motor of unusual power and smoothness, for quick, clean cutting, even with the larger sizes of transplant cutters. A convenient finger control switch gives you instant start or stop of the trephine blade. Light weight, beautifully, precisely built and balanced, the trephine is furnished complete in a fitted case with two cutting blades (1.5 mm. and 2 mm.) and including a special long-life battery box. *Save $25.00! Special. Each $72.50*

THE WITZEMAN BUR—A round, medium size (0.9 mm.) corneal bur mounted on a short shank that is interchangeable with the Green-type cutting blades on the Mueller Electric Trephine. A very useful and efficient instrument for the removal of stains, rings, etc., following extraction of ocular foreign bodies. (Other sizes, special, to order.) Each, $5.25

*Instrument Makers To The Profession Since 1895*

**V. Mueller & Co.** 330 SOUTH HONORE STREET CHICAGO 12, ILLINOIS

# Complete ARTIFICIAL EYE Service

Experience gained through over 100 years of artificial eyemaking enables us to produce and fit the very finest in artificial eyes. Glass and plastic eyes made to order or available from stock. Eyes fitted to all types of motility implants

**artificial eye selection through the mail**

Orders filled the same day received
Eyes sent on memorandum
Liberal assortment of either glass or plastic
Samples accurately matched
Superior quality eyes—Finest workmanship

WRITE FOR FREE COLOR CHART AND SIZE GUIDE

*Serving the Profession Since 1851*

**Mager and Gougelman inc.**

30 North Michigan Avenue, Chicago 2, Illinois : 510 Madison Avenue, New York 22, New York

DETROIT • CLEVELAND • KANSAS CITY • MINNEAPOLIS • ST. LOUIS
BOSTON • PHILADELPHIA • PITTSBURGH • WASHINGTON

# *It's NEW... It's gay...*

# *It's the* **Cabaret**

with exclusive
WIRE CORE
CONTOUR TEMPLES

| Eyes | Bridges |
|---|---|
| 42 | 20 |
| 44 | 20, 22 |
| 46 | 20, 22 |

ON MECHANICAL CENTER

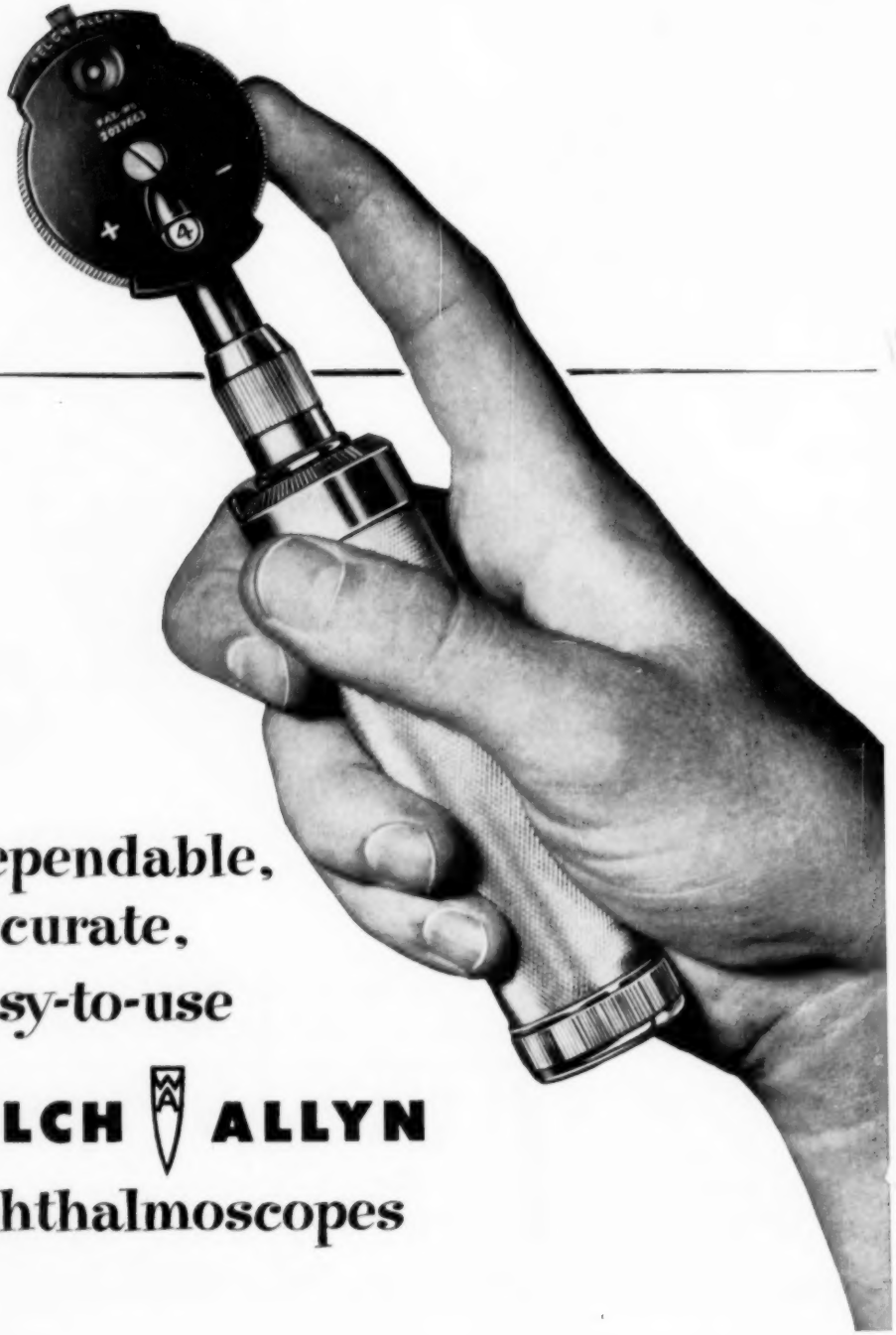
- For your patient's sake . . . prescribe an extra pair

Truly inspired styling, influenced by the newest trend in exotic frame design. In a colorful collection of solids . . . And in distinctive, new maze colors: Coco, Blue, Rose, Charcoal (in two-tone and overall). Tinsels are available.

AVAILABLE ONLY THROUGH YOUR PRESCRIPTION AND SUPPLY HOUSE

**ZYLO WARE CORP.** 11-15 47th Avenue . . Long Island City I, N. Y.

# Partner in your practice



Dependable,
accurate,
easy-to-use

**WELCH ALLYN**
Ophthalmoscopes

We wanted to be as modern
with our greetings as we are
with our frames . . .
but find, after all, there really
is no better way to express
the sincerity of our wishes than
just to say in the old, old way:

# Season's Greetings!

Away with ye Konoptics - we've Christmas wishes to bring

Al Kono & staff